Pharmacodynamics of vecuronium bromide in anaesthetized neonates, infants and children

(Farmacodynamiek van vecuronium bromide in pasgeborenen, zuigelingen en oudere kinderen onder anesthesie)

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Pharmacodynamics of vecuronium bromide in anaesthetized neonates, infants and children

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Aan mijn ouders
Aan Henkjan en Nienke

Page

ABBREVIATIONS

Cl	total plasma clearance
$Cp_{ss(50)}$	plasma concentration of a neuromuscular blocking drug at steady state of 50% blockade
ECG	electrocardiography
ED_{50}	effective dose of neuromuscular blocking drug resulting in a maximal blockade of 50%
ED_{90}	effective dose of neuromuscular blocking drug resulting in a maximal blockade of 90%
ED_{95}	effective dose of neuromuscular blocking drug resulting in a maximal blockade of 95%
EMG	electromyography
FS-EMG	frequency-sweep electromyography
GFR	frequency filtration rate
MAC	minimum alveolar concentration
MMG	mechanomyography
MRT	mean residence time
PEEP	positive end-expiratory pressure
RVD	relative volume of distribution
T_1	first twitch compared to control
T ½ alpha	plasma concentration decay rate during distribution phase
T ½ beta	plasma concentration decay rate during post-distribution phase
TOF	train-of-four
Vd_{ss}	distribution volume of steady state

I INTRODUCTION

In 1811 Brodie published his article on the different modes in which death is produced by certain vegetable poisons. He described how Woorara, a poison with which the Indians of Guiana armed their arrow heads (fig. 1), was applied to a wound on a guinea pig, causing it to become motionless whilst the heart continued to beat. Brodie found that artificial respiration prolonged the heart function for a short while. He concluded that the poison acted in some unspecified way on the brain and that cessation of the function of this organ was the immediate cause of death (Brodie, 1811).

HOG-ARROW.

Fig. 1 Hog-arrow

In 1812 he told the Society for the Improvement of Animal Chemistry, and via them the Royal Society, that he had kept a cat alive after administration of Woorara by artificially ventilating the animal for several hours. The cat was given to a friend and lived for some years thereafter. This experiment was repeated on an ass, which was ventilated for more than one hour by means of a pair of bellows and a tube introduced into the trachea. Having survived this, the animal was allowed to range on an island and was named Wouralia. "Wouralia shall be sheltered from wintry storm and when summer comes, she shall feed in the finest pasture. No burden shall be placed upon her and she shall end her days in peace". Wouralia died on the 15th of February

1839, having survived the operation almost 25 years earlier (Brodie, 1851; Waterton, 1839).

Woorara was also known as "ourari". In the language of the Tupi Indians this word means "the poison with which one can kill birds". Later it became "curare". Alexander von Humboldt was the first to describe in detail how the poison was prepared from the barks of the creeper Chondodendron tomentosum and Strychnos toxifera. The poison was stored and transported in bamboo tubes, hence the name tubocurarine.

In the mid-1850's Virchow and Thibeaud, and Vulpian performed a number of animal experiments for the purpose of investigating whether curare and strychnine neutralize one another. Vulpian's conclusions were that curare is not a direct antidote for strychnine and neither is strychnine a direct antidote for curare; and that in the case of tetanus, curare would merely add another hazard in the presence of a prognosis which was already grave (Vulpian, 1857).

Claude Bernard performed his classical experiments on frogs in 1854 and published these reports in 1857. He observed that motor nerves alone were affected and that the sensory nerves were spared (Bernard, 1857) (fig. 2).

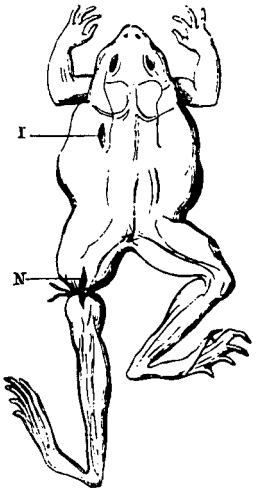


Fig. 2 Frog, experiment C. Bernard

In 1932 West reported on the hypodermic administration of curare to thirty patients, seventeen of whom he described, including patients suffering from epilepsy, rigidity due to pyramidal lesions and Parkinsonism. The first paediatric patient to receive curare was described: "... a girl aged 13 with a right-sided hemiplegic contraction, lasting since birth. Spontaneous athetoid movements occurred from time to time and the arm would take up unusual postures sometimes for a considerable period. Curare in increasing doses up to 12 milligrammes was given and it was not until this dosage was reached that symptoms were noticed. The injection was followed by nystagmus on fixing the eyes to the left. There was no diplopia. The child was a little giddy on walking, the arm hung almost flaccid by the side. Passive flexion encountered no resistance, extension was met by a temporary clasp knife rigidity, which gave way to allow full extension in a manner which had not been possible before. The first dose in this case produced a marked fall in blood pressure from 120/60 (pulse 74) to 94/60 (pulse 60) and this hypotension remained for over twelve hours. Four days later the blood pressure was 122/64 and the pulse 84. Cardiac extrasystoles occurred when the pulse-rate was at its lowest ...".

West considered his communication to be, from the therapeutic point of view, both preliminary and tentative. Yet he forecasted a place for curare in therapeutics and pleaded for more research and purification of curare (West, 1932). In 1938 West reported that curarine caused a bronchial spasm, resembling that caused by histamine. As an antidote for bronchial spasm, bradycardia and hypotension adrenalin was used (West, 1938).

In 1940 Bennett published a report on how traumatic complications in convulsive shock therapy were reduced by intramuscular or intravenous injections of an infusion or an alcoholic extract derived from crude curare. He used this technique on a large number of spastic paralytic children. As antidote he advised epinephrine and neostigmine (Bennett, 1940).

The introduction of curare into clinical anaesthesia was reported by Griffith and Johnson in 1942 with their publication: "The use of

curare in general anesthesia". Intocostrin, a water soluble extract of unauthenticated curare, was given intravenously in a dosage of 10-20 mg of the active curare per 20 lbs (9 kg) of body weight. It produced a rapid and "complete" muscular relaxation within one minute, gradually disappearing over 10-15 minutes. None of the 25 patients showed any evidence of serious depressing effects on respiration, pulse or blood pressure. A second injection on the same day required a smaller dose. All patients underwent inhalation anaesthesia with neostigmine used as an antidote for the curare. They warned against its somewhat fleeting action and stressed that in no sense could Intocostrin be considered as an anaesthetic agent. It should be used only by experienced anaesthetists in well-equipped operating rooms (Griffith, Johnson, 1942).

In the Netherlands F. Van Nouhuys from the Red Cross Hospital in The Hague first used curare in anaesthesia in 1946 (Van Nouhuys, 1947). He warned against the differences in potency between the two available curares: Intocostrin and Myostatin. He stated that curare is non-narcotic and advised the use of reduced dosages in children. In October 1946 Myostatin was also introduced in the 'Wilhelmina Gasthuis' in Amsterdam by Mrs. Vermeulen-Cranch. According to Mauve (1948) by November 1947 175 curare-anaesthetic procedures had taken place, with the youngest patient being 16 years old.

Almost immediately after the introduction of curare into anaesthesia practice by Griffith, the use of the drug was extended to the paediatric age group; such was the case in the Sophia Children's Hospital (fig. 3). In adult anaesthesia these advancements contributed greatly to extending surgical possibilities. For example the muscle relaxation achieved with curare assisted the surgical course, especially in the case of laparotomies, thoracotomies and orthopaedic procedures. This of course was also true for paediatric surgery, which was still a very young surgical discipline. Despite the fact that Socrates (470-399 B.C.) had asked his fellow Athenians: "Why do you gather riches and care so little for the children to whom you will have to leave it all?", Hippocrates (460-377 B.C.) had pointed out special features of diseases in childhood and Celsus (25 B.C. - 50 A.D.) had stated that children should be treated entirely differently

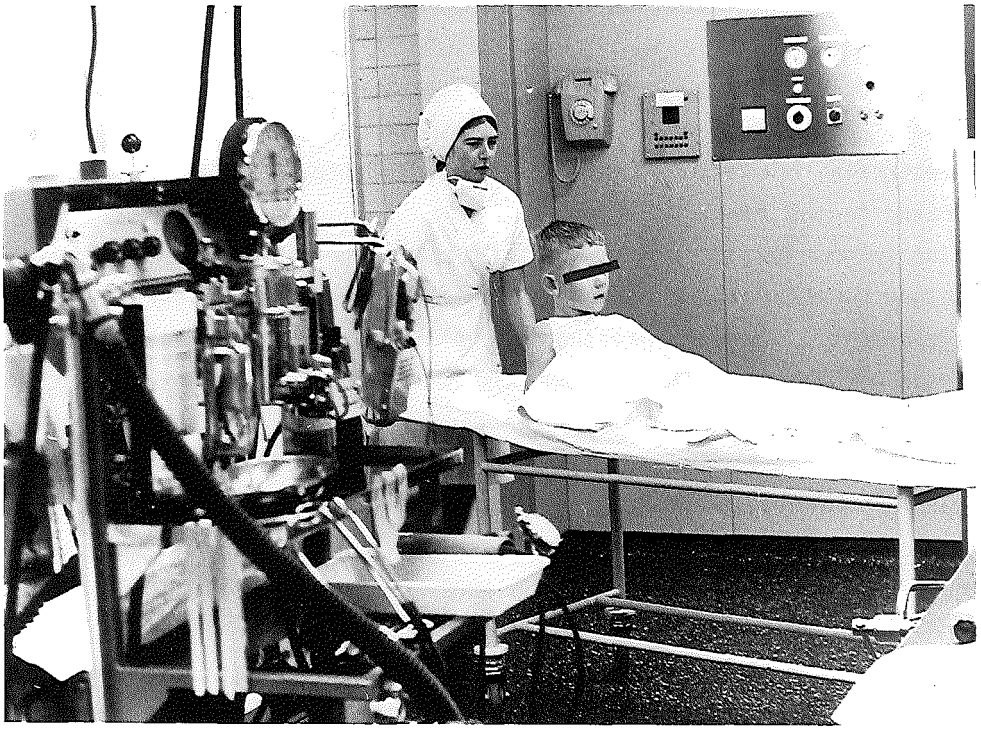


Fig. 3 Operating Room, Sophia Children's Hospital, circa 1970

from adults, it took almost 2000 years before physicians began to take interest in neonates, infants and children. The cause for this long delay may lie with Soranus (98-117 A.D.) who relegated the diseases of infants and children to the area of midwifery. In the meantime it were the barber-surgeons, although not accepted as physicians, who took care of the infants and children. Although not very capable in treating and curing, some described congenital anomalies and produced beautiful drawings (Van Meekeren, 1611-1666, reprint 1979).

The English physician George Armstrong was a rare exception. In 1769 he opened his Dispensary for Children (mainly for the poor) in Holborn (London). Although he was met with abuse by his colleagues, his entire life was devoted to the care of sick children. Nobody took up his cause when he died, until in 1802 when the first Hospital for Sick Children was opened in Paris. Armstrong has left us a treatise on paediatrics.

During the Nineteenth Century many more children's hospitals were founded and, at last, surgery became acccepted as a medical profession; with appointments of the first paediatric surgeons. Closely integrated with the developments in surgery, paediatrics, anaesthesia, biochemistry, radiology and pathology, paediatric surgery thrived in the Twentieth Century.

The mortality rate for paediatric surgery early in the Nineteenth Century remained as high as 40-60 %. Improvement was achieved with the development of modern anaesthesia and the discovery of antisepsis by Lister in 1867. In 1953 Snyder and colleagues reviewed 66 cases of sudden cardiac arrest in children occurring in the operating room. As probable causes they mentioned anoxia and vagovagal reflex. This was a major step forward since many sudden deaths under anaesthesia had previously been attributed to "status thymico-lymphaticus" until Professor Henry Cohen stated in 1939 that this was a meaningless term.

Snyder and colleagues noticed an alarming increase in the incidence of cardiac arrest between 1948-1953 and considered it to be a problem of anaesthesia. Simple open-drop technique had changed to the use of the anaesthetic machine with more dead space and respiratory resistance (Snyder et al., 1953). In the period between 1947 and 1956 the frequency of cardiac arrest associated with anaesthesia in infants was 1 in 600, in children 1 in 1700 and in adults 1 in 2500. Hypoxia and ether overdose were reported to be among the common causes (Rackow et al., 1961). Graff and coworkers stated that mortality from anaesthesia was five times greater in the paediatric age group compared with adults and that respiratory problems were implicated in 83% of these deaths(Graff et al., 1964).

Nowadays it is known that the respiratory physiology of the newborn differs from that of the adult. With an overall metabolism per kilogram bodyweight almost twice that of an adult and a lung surface area per kilogram approximately the same, a baby has less reserve of lung surface area for gas exchange to meet any increased metabolic demand. The closing volume in the neonatal lung is larger than the functional residual capacity, so airway closure occurs within normal tidal respiration.

Hypoxia in neonates may also result in additional effects not seen in older children. Severe metabolic acidosis is common due to the neonates increased capacity for anaerobic metabolism. Cerebral and pulmonary haemorrhage, severe hyperkalaemia and hypoglycaemia may also be associated with hypoxia. To worsen the situation, hypoxia and acidosis cause pulmonary constriction and, in the first few days of life, may result in the circulation reverting to the transitional circulation of the newborn with right to left shunting through the foramen ovale and ductus arteriosus. This in turn leads to further hypoxia.

Controlled ventilation ensures that adequate alveolar ventilation takes place and some positive end-expiratory pressure (PEEP) helps to maintain an adequate residual volume. Moreover, in neonates the minimum alveolar concentration (MAC) for halogenated agents is higher than the concentration that remains free from cardiovascular and ventilatory side effects. Thus, from an anaesthesia point of view, it is of great advantage to paralyse and ventilate the suckling. Nevertheless, it is still frequently stated that the use of relaxant drugs in neonates is contraindicated because they are unnecessary. Jackson Rees is, however, correct in pointing out that control of respiration is extremely desirable in infants (Jackson Rees, 1950).

Improvement in the paediatric endotracheal tube by Magill (1936) and the invention of the T-piece by Ayre in 1937 brought comparative peace to the operating theatre during operations for hare-lips and cleft palates, formerly the scene of many sanguinary battles (Ayre, 1937). The insight of Smith (1953) on how to prevent tracheitis in children following endotracheal anaesthesia reduced the number of undesirable side effects due to intubation.

The use of relaxants became well-established, with advantages including: improved surgical conditions, non-flammability and the possibility to operate on a motionless patient during a shallower stage of anaesthesia. As the safety factor associated with anaesthetic agents diminishes with use in neonates, relaxation of the patient with d-tubocurarine therefore became a part of the famous Liverpool technique of anaesthesia in neonates and infants.

Originally only oxygen was added to curare for infant surgery, but

when Smith, after testing curare on himself, reported the complete absence of cerebral effects of the drug, meaning that patients were completely conscious when fully paralyzed, this technique was abandoned (Smith, 1947). Nitrous oxide was added and, together with oxygen and d-tubocurarine, formed the principal agent for anaesthetizing all infants and children whilst being ventilated (Jackson Rees 1950, 1958, 1960, 1965).

Research on muscle relaxants in adult and paediatric patients proceeded. Other relaxants were found and tested. The depolarizing neuromuscular blocking drug succinylcholine became popular, especially since Stead reported that infants had an increased tolerance to this drug (Stead 1955). In 1952 L.A. Boeré, head of the Department of Anaesthesia in Leiden, introduced Celocurin (succinylcholine iodide) in the Netherlands. He recommended dosages of 0.1-1.0 mg/kg i.v. as a bolus or in a drip, dependent on whether spontaneous respiration, or even a respiratory arrest was required. Indications for use of Celocurin were: endotracheal intubation, cholangio-, arterio- and angiography, electroshock and operations requiring relaxation. Of the 48 patients (age range 8-81 years) receiving Celocurin no difficulties were reported (Boeré, 1952). Subsequent disclosure that succinylcholine may cause severe bradycardia (Leigh et al., 1957), dual block (Churchill-Davidson et al., 1960) and prolonged apnea (Churchill-Davidson, 1959) reduced its popularity. Many anaesthetists returned to the use of the more predictable nondepolarizing neuromuscular blocking drugs. Baird and Reid (1967) published the first report on the use of pancuronium in anaesthetized patients. Thereafter, the use of many other relaxants, including vecuronium bromide, followed.

In 1955 Stead pointed out that the response of infants to the nondepolarizing muscle relaxant d-tubocurarine is different from that of adults. Infants showed an increased sensitivity. Although his "evidence" was based on experience with only two infants, the basic observation has been upheld by subsequent work and initiated an important line of investigations (Stead, 1955).

Churchill-Davidson (1963) measured the electromyographic response of

five neonates to decamethonium, a depolarizing neuromuscular blocking agent, neostigmine sulphate and edrophonium, both anticholinesterase drugs, antagonizing the effect of nondepolarizing muscle relaxants. He concluded that the neuromuscular transmission in the first few weeks of life differed from that found in adult patients and that the characteristics of the block obtained after decamethonium strongly resembled many of the features seen in patients with myasthenia gravis.

Research into the development of the neuromuscular system was also in progress (Buller, 1966; Koeningsberger et al., 1973). More articles were published on neuromuscular blockade in neonates, infants and children (Long, Bachman, 1967; Walts, Dillon, 1969; Zsigmond, Downs, 1971; Yamamoto et al., 1972; Nightingale, Bush, 1973; Goudsouzian, 1980; Cook, 1981). Despite all these efforts controversies remained as to whether children were more (Stead, 1955; Lim et al., 1964; Long and Bachman, 1967), equal (Goudsouzian et al., 1974) or less (Goudsouzian et al., 1975) susceptible to the blocking action of the neuromucular blocking agents.

Difficulties are found in comparing results because of differences in the methods of measuring blockade (by force or by electromyography), differences in stimulation, muscles to be measured, calculated doses (by kg bodyweight or m^2 body surface) anaesthesia techniques (use of halogenated agents or not), body temperature, arterial PCO_2 and others. Last but not least, the actual drug studied also varies among the many publications.

Nowadays, clinical anaesthesia is inconceivable without the use of muscle relaxants. Nevertheless the problems associated with the pharmacodynamics of the drugs in neonates, infants and children still needs further investigation. Working daily with the young, we decided to undertake another study on the effects of a modern nondepolarizing relaxant drug, vecuronium bromide, in the various paediatric age groups. In order to compare the results we strived to keep as many parameters as possible constant, using a uniform anaesthesia technique, avoiding drugs known to influence neuromuscular transmission, and studying patients without metabolic or neuromuscular diseases.

Hopefully this study will contribute to the understanding of the pharmacodynamics of vecuronium in these different age groups.

II NEUROMUSCULAR BLOCKING AGENTS IN THE PAEDIATRIC AGE GROUP

Since the first use of neuromuscular blocking agents in children controversies, including the correct dosage required, have remained. Many objections were based on the contradictions involved. Neonates, infants and children, depending on the respective outcomes of studies, were considered to be more, equal or less sensitive to these drugs than adults. The diverse conclusions reached by various authors depend to a great extent on the methodology used for investigation of the compounds. Various ways were used to define the effect: apnea, ability to control respiration, ease of endotracheal intubation and more increasingly sophisticated monitoring techniques.

QUANTITATIVE MONITORING OF THE NEUROMUSCULAR FUNCTION

Evoked electromyography (EMG), the technique chosen for our study, was first used by Harvey and Masland in 1941. They stimulated the ulnar nerve electrically and recorded the electrical response of the abductor digiti minimi muscles. Another possible technique is the recording of the mechanical response by mechnomyography (MMG). With MMG the clinically important muscle contraction (excitation-contraction coupling etc.) is also included in the measurement, whereas with EMG only the neuro-muscular transmission part is measured. The best approach for an in vivo nerve-muscle preparation is by stimulating the ulnar nerve and recording the force of adduction of the thumb by the adductor pollicis brevis muscle. The advantage of using evoked responses is that the cooperation of the patient is not necessary and the stimulus is standardized. Thus this method is very suitable for patients under anaesthesia. In paediatrics, mechanomyography is complicated by the bulkiness of the equipment and thus electromyography is the technique of choice.

The action potential and contraction of a single muscle fibre is of an "all or nothing" type. Increase in contraction force or action potential amplitude of a muscle is due to an increase in the number of participating contracting muscle fibres (recruitment). For measuring EMG or MMG supramaximal stimulation is always used. All possible fibres must be excited to exclude interference by recruitment.
Another important factor is the type of stimulation. The stimuli should be 0.1-0.2 msec in duration. If the duration of a stimulus exceeds 0.2 msec the refractory period is exceeded and a second action potential may occur. The ideal electrical impulse is a square wave rectangular (Epstein et al., 1969). The stimulus frequency has a major influence on the obtained results, especially when the frequency is high (Ali, Savarese, 1980). The most commonly used stimulustypes are:
- single twitch at slow rates (0.1-0.2 Hz)
- train-of-four stimulation (2 Hz for 2 seconds)
- tetanic stimulation (50 Hz for 5 seconds)

Single twitch rates are useful whenever there is a control response, taken before administration of the muscle relaxant. By comparing the percentage of change in twitch tension or EMG amplitude (deflection) due to the relaxant, a percentage value can be obtained, indicating the degree of paralysis. Relatively high degrees of acetylcholine receptor occupation are detected by this method.
Depression of twitch response can only be observed if more than 75% of the postsynaptic receptors are blocked. When 90% or more are occupied, a state of complete paralysis exists (Waud, Waud, 1972). A higher dose of relaxant is required to depress the twitch height when the stimulus frequency decreases. At high frequencies there is depletion of acetylcholine and consequent fading in response. This is more pronounced and occurs at a lower frequency in relation to the age of the children.

The train-of-four consists of four supramaximal stimuli applied at a frequency of 2 Hz. There is fading in the responses when a nondepolarizing relaxant drug is administered. The ratio of the amplitude of the fourth twitch to the first is used for assessment of superficial neuromuscular blockade. The fourth response in the train is eliminated at approximately 75% depression of the first twitch. The third and

fourth twitches are abolished at 80% suppression of the first twitch while, in addition, the second twitch becomes undetectable at about 90% block of the first twitch. Thus for clinical purposes merely counting the number of twitches in the train-of-four response makes it possible to quantify the extent of a more pronounced blockade (Ali, 1985). A rate of 2 Hz is rapid enough to produce depletion of the immediately available stores of acetylcholine, yet slow enough to prevent transmitter release and synthesis facilitation. Four stimuli were chosen because the fourth response is maximally depressed during partial nondepolarizing neuromuscular blockade. Thereafter the twitch height levels off.

There is a linear relationship between single twitch and train-of-four values. Goudsouzian and colleagues found this correlation for vecuronium in children (2-17 years of age) during recovery to be very good (Goudsouzian et al., 1983a). Correlations between EMG single twitch and train-of-four are varying. Differences are found between onset and recovery of blockade and between different blocking agents (Calvey et al., 1983, Goudsouzian et al., 1983b).

In children anaesthetized with halothane without administration of muscle relaxants the components of the train-of-four are practically equal in size, thus the train-of-four ratio is 100%. In infants less than one month of age the train-of-four ratio is 95% (Goudsouzian, 1980) and in premature infants 83% due to spontaneous fading in response (Goudsouzian et al., 1981). This difference in baseline causes difficulties in comparing the effects of neuromuscular blocking agents using this technique in different age groups, including neonates.

Tetanic stimulation increases mobilization and enhances synthesis of acetylcholine to a limited degree. If the duration of the stimulus is too long or if the frequency is too high, spontaneous fade occurs. Fade is more marked in neonates and especially in premature infants (Churchill-Davidson, Wise, 1963; Koenigsberger et al., 1973).

VARIOUS FACTORS

Previous studies reported no statistically significant difference in

the time to 95% twitch depression with needle or surface electrodes (Stiffel et al., 1980; Capan et al., 1981). For proper interpretation of mechanomyography, attention should be paid to the capacity of the force transducer, the relation of the transducer to the direction of movement of the muscle studied, the initial muscle tension and avoidance of the contribution of direct muscle response to the measurement. Electromyography is difficult and expensive for everyday clinical monitoring of neuromuscular function, but more suitable apparatus have now been developed for routine clinical use (Carter et al., 1986; Harper et al., 1986; Pugh et al., 1984). The principal techniques for examining the EMG are measurement of the EMG peak height and the surface area by integration of the EMG response. Both approaches of the analysis have been published (Ali et al., 1971; Lam, Cass, 1981). The correlation between the two methods is extremely close (r=0.976) (Pugh et al., 1984). Evoked electromyographic and mechanical responses of the adductor pollicis generally show a good correlation (Crul et al., 1983). A difference however can be observed. This difference is drug-specific and is more pronounced during onset of blockade than during its antagonism by neostigmine (Harper et al., 1986).

FACTORS INFLUENCING THE MECHANISM OF ACTION OF NONDEPOLARIZING MUSCLE RELAXANTS

Suxamethoniumchloride, a depolarizing relaxant, is frequently used to facilitate intubation of the trachea whereafter a nondepolarizing agent is administered to relax the patient during surgery. Prior administration of suxamethonium enhances the neuromuscular blocking effect of non-depolarizing blocking agents (Walts, Dillon, 1969; Katz, 1971; Buzello et al., 1983). It augments both the degree and duration of the blockade induced by vecuronium (Krieg et al., 1981; D'Hollander, 1983).

Hypothermia influences the effect of neuromuscular blocking drugs. Studies show a species-dependent difference. For example, the conduction velocity in the nerve axon during hypothermia is increased in the

squid axon (Hodgkin, Katz, 1949) and is unchanged in the frog sartorius preparation (Katz, Miledi, 1965). The sensitivity of the postjunctional receptors to transmitter is decreased, unchanged or increased in different species (Zink, Bose, 1974; Thornton et al., 1976). The response of directly stimulated muscle during hypothermia is also variable in different species. The mechanism of the effect of hypothermia on the interaction of muscle relaxants with the neuromuscular function is complex.

In cats Miller et al. (1975) found hypothermia to augment a d-tubocurarine blockade. Ham et al. (1981) studied humans during hypothermia. They reported that pharmacokinetic variables were not significantly affected. No difference was found in the steady-state serum concentration that resulted in 50% paralysis during hypo- or normothermia. They concluded that the sensitivity of the neuromuscular junction of d-tubocurarine is not affected by hypothermia. In a few patients there was a marked delay in onset time. Remarkable was that spontaneous recovery of neuromuscular function, measured by EMG, was similar, but measured by MMG was prolonged in the hypothermic group.

Buzello and collegagues (1985) studied alcuronium, d-tubocurarine, pancuronium and vecuronium during (hypothermic) cardiopulmonary bypass using EMG and MMG. Hypothermic cardiopulmonary bypass attenuated alcuronium, d-tubocurarine and pancuronium neuromuscular blockade. Vecuronium neuromuscular blockade was enhanced, vecuronium was no longer a shorter-acting agent than pancuronium under these circumstances. The difference in response may be explained by a direct effect of hypothermia at the neuromuscular junction, rather than by pharmacokinetic factors related to bypass. The EMG is more sensitive than is the MMG in reflecting the effect of changing body temperature on neuromuscular transmission (Buzello et al., 1987). One concludes that, in order to compare pharmacodynamic data in different age groups, the body temperature must be kept normal and constant.

Hypercarbia and hypocarbia have been studied in relation to pancuronium-induced neuromuscular blockade. Wirtavuori and colleagues showed recovery after neostigmine to be slower in hypoventilated patients with MMG. This effect, however, was not seen using EMG amplitude

(Wirtavuori et al., 1982). This finding was interpreted as evidence for the direct depressant effects of carbon dioxide on contractility. Lee and Katz (1980) claimed the EMG amplitude to be a better indicator of actual neuromuscular blockade than measurement of twitch tension in this situation. Gencarelli and coworkers (1983) studied pancuronium and vecuronium using MMG. Hypocarbia and hypercarbia, induced before a single dose of either drug was given, had little effect on pancuronium and vecuronium dose-response relationships and recovery rates (recovery from 75-25% block). Acutely induced hypocarbia caused an increase and hypercarbia a decrease in control twitch tension. During partial pancuronium or vecuronium neuromuscular blockade, hypocarbia induced an increase in twitch tension. Acute hypercarbia caused a significant decrease in twitch tension during a partial vecuronium blockade.The observed effect was much larger than the decrease observed for pancuronium. The conclusion must be that the neuromuscular junction is not the main side where hypercarbia effects evoked twitch contraction.

Metabolic changes in acid-base balance

Most workers found that metabolic acidosis or alkalosis affect the action of d-tubocurarine in the same way as respiratory acidosis or alkalosis. But the neuromuscular block produced by gallamine was affected the opposite way, being antagonized by respiratory acidosis and potentiated by respiratory alkalosis. These effects are usually attributed to changes in the binding of gallamine to plasma proteins. (Katz et al., 1963; Crul-Sluyter and Crul, 1974; Miller and Roderick, 1978).

In vivo studies in the cat showed a significant antagonism of vecuronium by metabolic alkalosis, whereas metabolic acidosis caused a potentiation of the MMG quantitated blockade (Funk et al., 1980).

Antibiotics and neuromuscular function

Antibiotics may enhance the neuromuscular blocking properties of muscle relaxants. However there are many differences in quality and

quantity. That the effect can be of serious clinical significance was first reported by Pridgen in 1956. Antibiotics were classified according to Weinstein, rather than by the incompletely understood mechanism by which they produce neuromuscular block (Sokoll, Gergis, 1981).

1. Drugs inhibiting synthesis of bacterial cell wall.

In terms of producing a neuromuscular blockade, antibiotics of this group are the safest. Penicillin blockade, if it occurs, may be reversed by calcium, but is unaffected by neostigmine. This suggests that the probable site of action is at the prejunctional nerve terminal.

2. Agents affecting the permeability of the cell membrane.

Polymycins and colistin are examples of this group. They cause a blockade of complex origin, predominantly postsynaptic, which is not reversed by calcium or neostigmine. 4-Aminopyridine will reverse the block (Lee, de Silva, 1979).

3. Agents inhibiting protein synthesis.

There are two groups of such agents. The first and most important group for enhancing neuromuscular blockade includes the aminoglycosides (streptomycin, neomycin, kanamycin, gentamycin) and the lincosamides (lincomycin, clindamycin). They show a wide range of activities. Most of these drugs have combined actions on both nerve terminal and the cholinergic receptor, can be reasonably well reversed by calcium and partially reversed by neostigmine (Albiero et al., 1978; Singh et al., 1982; Booij et al., 1978). The second group consists of tetracyclin and oxytetracyclin. Both drugs possess weak and clinically insignificant neuromuscular blocking properties. The mode of action in producing neuromuscular block has not been completely elucidated. The blockade is usually reversible by calcium, but not by neostigmine (Singh et al., 1978; Ibsen, Urist, 1962; Bowen, McMullan, 1975; Pittinger, Adamson, 1972).

McIndewar studied an interaction between vecuronium and some antimicrobial agents in the cat, using MMG (McIndewar, Marshall, 1981). A streptomycin-benzylpenicillin mixture causes a significant potentiation of the neuromuscular blocking activity of vecuronium. An apparently specific potentiating interaction was observed between vecuro-

nium and metronidazole. Krieg et al. (1980) studied neomycin, gentamycin and clindamycin in combination with vecuronium. The dose-response curve of vecuronium shifted to the left but in clinical dosages the time-course of the effect of a bolus dose of vecuronium was unaltered.

Volatile anaesthetic agents

Many studies have demonstrated an increase in the magnitude and duration of nondepolarizing neuromuscular blockade by volatile anaesthetic agents. Confusion concerning potentiation does not exist. Most investigators used MMG (Rupp et al., 1984; Waud, 1979), but EMG produced the same results (Stirt et al., 1983; Lee et al., 1984). Differences between species do not exist in this regard. Human and animal studies, both in vitro and in vivo, all show a dose-dependent potentiation in the magnitude of blockade of many different nondepolarizing neuromuscular agents caused by many different volatile anaesthetics. In addition, Stanski et al., (1979) reported that halothane does not alter the pharmacokinetics of d-tubocurarine.

Vecuronium was investigated by Foldes et al. (1980), Nagashima et al. (1981), Duncalf et al., (1983), Lee et al., (1983, 1984) and Rupp et al., (1984). All authors found potentiation, a shift to the left of the dose-response curve. But Rupp et al. (1984) found potentiation of vecuronium to be less dependent on the concentration of volatile agents than that of pancuronium. Enflurane potentiates most, followed by isoflurane and then halothane. The recovery rate (75-25% blockade) is also prolonged (Lee et al., 1983). Enflurane without a relaxant drug also has effect on neuromuscular transmission: the twitch response decreases, fade and posttetanic facilitation occur. These effects cannot be antagonised by neostigmine (Lebowitz et al., 1970).

Several mechanisms have been proposed by which volatile anaesthetic agents produce relaxation and augment the neuromuscular blockade from muscle relaxants. However the exact mechanism has not yet been elucidated. One theory is that normally the equilibrium between normal resting and desensitized states of the receptors favors the former, making receptors available for acetylcholine binding and causing

neuromuscular transmission. This equilibrium is altered by volatile anaesthetics, which encourage formation of the desensitized state and reduce the number of available resting receptors, thus weakening neuromuscular transmission and anhancing the action of nondepolarizing agents (Standaert, 1984).

Concerning all the factors influencing the neuromuscular junction and neuromuscular blocking agents, it is not surprising that comparison of the results from various studies is difficult (Miller, 1986). Moreover many more drugs may interfere with nondepolarizing relaxants, some very important, some clinically irrelevant, as reported by Katz (1985). In experimental settings it is easy to avoid such drugs, but not clinically. For example it is difficult to anaesthetize very young children without the use of volatile agents when they cannot be completely relaxed, such being the case when dose-response curves or recovery are studied. Most neonates requiring surgery, have some metabolic disturbances or receive antibiotics. Thus to avoid differences when comparing the effect of neuromuscular blocking agents in different age groups, it is essential to exclude such patients from the studies.

Comparison of different studies may also be hampered by the use of different neuromuscular blocking drugs. In some of these drugs prejunctional effects may be of more importance than in others (Blaber, 1973; Bowman, 1980a; Stanec, Baker, 1984). At slow rates of motor nerve stimulation it is easier to detect the "static" postjunctional effects. However, if one studies the "dynamics" of synaptic transmission using near-physiological rates of stimulation (20-50 Hz), failure of the various prejunctional functions is revealed (Galindo, 1972).

Pancuronium possesses prominent postjunctional effects but more recent studies indicate that it has significant prejunctional actions (Su et al., 1979), a long-established fact for d-tubocurarine (Lilleheil, Naess, 1961). Torda and Kiloh (1982) found in the toad sartorius preparation that ORG NC 45 (vecuronium) reduces the main quantal content of the end-plate potential as well blocking postjunctional receptors. Another consideration is the difference found in the relation between single twitch and train-of-four ratio during

onset and recovery of the blockade. The fade of the trains is much more marked during recovery than during onset in a vecuronium blockade (Bowman, 1980a).

Comparing the effects of muscle relaxants in children of different age groups gives additional problems to the ones already described. For the past 30 years investigators have attempted to ascertain whether the responses of the newborn infant to nondepolarizing muscle relaxants do indeed differ from those in the adult, and to define the possible causes for these differences.

Throughout childhood there is physical and biochemical maturation of the neuromuscular junction, change in the properties of skeletal muscle and an increase in the relative amount of muscle as a proportion of body weight. But at the same time the apparent volume of distribution, and possibly the metabolism, the redistribution and the clearance of relaxants also change. Since all these factors can influence pharmacodynamics and pharmacokinetics it is not surprising that the neonate's responses to relaxants have not yet been definitively clarified.

MATURATION OF THE NEUROMUSCULAR SYSTEM

At 7.5 weeks gestational age the human foetus starts to move. These first movements may not be initiated by a nerve action but by activity of the muscle itself (Joppich, Schulte, 1968).
At 11 weeks motor nerves reach the muscle cells of the biceps muscle and at 12 weeks the muscles of fingers and toes. At 26-28 weeks gestational age the motor nerve ends differentiate into the later motor end-plates. The structural and functional development of the neuromuscular system is incomplete at birth (Cook, 1981). The human myoneural junction has by then developed postsynaptic infoldings and some degree of ramification. Only by 2 years of age has the myoneural junction complete ramification and segmentation as in the adult (Juntunen, Teravainen, 1972).

The differentiation of muscle fibres proceeds along the histogenetic course: from myoblasts via myotubes to mature muscle fibres. The criteria used for differentiation vary slightly from author to author.

Since development is a continuous process, intermediate forms may be observed (Buller, 1966). The myotubes progress to the stage of mature muscle fibres with the migration of the centrally placed nuclei to the margins of the fibre. The pale axial cytoplasm disappears, its place being taken by newly formed myofibrils which ultimately fill the mature cell. So the tubular appearance of the myotubes is lost. This transition from myotube to mature muscle fibre occurs in the latter part of intra-uterine life and in the first few weeks after birth (Buller, 1966). The proximal muscles are the first to develop. There is a subsequent progressive proximo-distal differentiation, the muscles of the hand and foot being the last to form. The muscles of the hand differentiate slightly earlier than those of the leg.

As early as in 1678 Lorenzini divided skeletal muscles of warm blooded beings into two groups: red and white. In humans such a marked difference does not exist (Joppich, Schulte, 1968). In man all of the skeletal muscle consists of a mixture of two basic fibre types, type I and II. The relative proportions vary from muscle to muscle. Type I fibres have a high concentration of the oxidative enzymes concerned with aerobic metabolism. They belong to motor units which, when activated, develop a relatively slow and sustained, tonic contraction. Type II fibres have a high concentration of myosin ATPase and of glycolytic enzymes such as phosphorylase. These fibres, when stimulated, generate a more rapid and less sustained, phasic contraction. Type II fibres can be subdivided in two types, IIA and IIB and in the immature muscle also in IIC on basis of their myosin ATPase activity at different pH's and levels of oxidative enzyme activity, Type IIA is fast oxidative glycolytic and type IIB is fast glycolytic. Type IIC fibres show a myofibrillar ATPase staining still present at pH 4.3.

A clear subdivision into the two histochemical fibre types cannot be made with certainty until between the 18th and 20th weeks of gestation. Prior to the 19th week there is a uniform population of fibres in the vastus lateralis with the staining characteristics of type IIC fibres. During the last three months of pregnancy their number decreases progressively and type IIA and IIB fibres appear in the pattern of mature human muscle. From weeks 20-26 only a small

proportion of the fibres show the characteristics of type I. After 26 weeks there is a progressive increase in numbers of type I fibres and from 30 weeks gestation to full term the muscles show a chequerboard pattern similar to that of mature adult muscles with approximately equal numbers of type I and type II fibres (Mastaglia, 1981).

With maturation of muscle fibres some slow-contracting muscle is progressively converted to fast-contracting muscle with a concomittant change in the force-velocity relationship. However, in both the diaphragm and the intercostal muscles in infants an increase in the percentage of slow muscle fibres occurs in the first month of life; thus conversion of muscle types can go in both directions (Keens et al., 1978). There appears to be considerable variation in the exact timing of this change, not only from species to species but also from one muscle to another in the same animal (Buller, 1966). Even in adults, where all muscles are mature, it is not possible to apply observations made in one muscle to other muscle groups (Weber, 1984). Studies have been made on different muscle groups by various investigators and many differences between onset time and sensitivity to neuromuscular blocking agents have been observed (Wymore, Eisele, 1978; Lebrault et al., 1985; Donati et al., 1986; Pathak et al., 1986). The major physiologic differences found between muscle types correspond, to a large extent, to the relative ratios of fast to slow muscle fibres found in the muscles (Weber, Muravchick, 1986). Most muscles are mixtures of these fibres, generally ranging from 30-90% slow fibres (Johnson et al., 1973). Even in the hand considerable differences are found. The human adductor pollicis muscle contains approximately 80% slow fibres and the abductor digiti minimi about 52% slow fibres.

Neuromuscular transmission depends on four main factors:

- the quantity of acetylcholine released by each motor nerve inpulse
- the sensitivity of the post-junctional cholinoceptor to acetylcholine
- the excitation threshold of the muscle fibre membrane adjacent to the end-plate region
- the level of activity of the acetylcholinesterase present at the junction

The first factor may be subdivided into the number of acetylcholine quanta released by each nerve impulse and the amount of acetylcholine contained in each quantum. Recording of the amplitude of spontaneous miniature end-plate potentials provides information about the depolarizing action of a single quantum on the post-junctional membrane. End-plate potentials obtained in response to electrical stimuli are used to estimate the average quantum content (Hubbard et al., 1969). Normally motor nerve endings release more acetylcholine than is required to ensure action potential formation in skeletal muscle. This is termed the safety factor. The size of the safety factor depends on the depolarisation produced by each quantum of acetylcholine, the number of quanta released by each nerve impulse and the difference between the resting membrane potential and the excitation threshold potential of the muscle fibre.

In rats of 110 days old the miniature end-plate potential was found to be half of that found in rats of 30 days old. The number of quanta released by each nerve impulse was 2.5-3 times as much in rats of 110 days old as in rats of 30 days old. There was no difference in resting membrane potential. The resulting calculated safety factor in rats of 30 days old was 70-80% that of 110 days old rats (Kelly, Roberts, 1977). If extrapolation from rat experiments to human is valid, these results suggest that infants will have a lower safety factor than adults and will therefore be more sensitive to nondepolarizing relaxants.

The development of acetylcholine receptors on muscle fibres has been studied extensively. In the cultured and embryo muscle fibres most of the acetylcholine receptors are diffusely distributed and freely mobile within the cell membrane. Some focal hot spots have an increased sensitivity. The establishment of nerve-muscle contact causes the immobilization of a dense cluster of receptors in the postjuntional membrane at the neuromuscular junction. The extra junctional receptor formation is depressed and the extrajunctional sensitivity to acetylcholine decreased (Bowman, 1980). In the human upper arm the period from the initial contact between axons and myotubes through the appearance of secondary postjunctional folds occurs between weeks 10 and 16 of gestation.

Acetylcholinesterase activity first appears as a diffuse stain in myotubes at embryonic stages. As the neuromuscular junction forms, the activity of acetylcholinesterase is localized to the synaptic gutter, the intercellular space between axon and Schwann cell and the nuclear envelope and tubular reticulum of both myotubes and Schwann cells (Carry, Morita, 1984).

In neonates EMG and MMG can both be used to study muscles. In 1963 Churchill-Davidson and Wise using EMG showed that at twitch rates of 0.25 Hz neuromuscular transmission is well maintained in neonates, but a tetanic rate of 50 Hz is poorly maintained. Ten years later Koenigsberger and coworkers (1973) made the same observation. Using EMG they found fading tetanus and post-tetanic exhaustion more marked in premature than in full-term infants. The latter having less myoneural reserve than older children and adults. Their data suggest that the infant neuromuscular junction may not be fully developed at birth and that maturation of the neuromuscular junction continues during neonatal development. Goudsouzian (1980) demonstrated a difference in neuromuscular transmission between neonates less than one month of age and infants and children aged between two months and nine years. He used EMG, but no blocking agents. All patients received halothane. Train-of-four ratio values increased significantly with age. Post-tetanic facilitation after 50 Hz stimulation was more marked in the group aged two months and older. There was also a significant negative correlation between age and contraction time. He concluded that maturation of neuromuscular transmission occurred in the first two months after birth. Crumrine and Yodlowski (1981) showed a measurable age-dependent difference between the myoneural function of infants less than 12 weeks old and that of older children and adults. They used the frequency-sweep electromyogram (FS-EMG) response pattern. By the age of 12 weeks the FS-EMG became adult-like. The diminished FS-EMG response in the high-frequency region of the younger infants indicates that these infants are unable to maintain a tetanic contracture because of failure in neuromuscular transmission. This provokes speculations that the margin of safety in the newborn is less than that in more mature individuals.

MATURATION OF THE KIDNEYS

The fetal kidneys produce diluted urine from as early as the third month of intrauterine life, although the excretory and regulatory requirements of the fetus are satisfactorily carried out by the placenta. At birth the kidneys must fully take up their role of excretion of the nitrogeneous end-products of metabolism and play a part in stabilizing the volume, osmotic pressure and chemical composition of extracellular fluid. Overall renal function is immature in the newborn. The glomeruli are smaller than in the adult, but their filtration surface in relation to body weight is similar. In relation to the extracellular fluid volume however, the filtration is less. The tubules are not fully grown and may not extend into the medulla. During the first few days after birth the function of the kidneys improves rapidly and there is a spurt of growth. This is partly caused by the increase in the total cardiac output the kidneys receive. The stimulus of birth causes the kidneys of the very premature infant to hypertrophy by developing new nephrons and increasing the glomerular surface area. The kidneys have full complement of nephrons by 36 weeks gestation, but there is a considerable heterogeneity in the extent of maturation of individual nephrons. The immaturity includes scant vascularity, short tubulus, low tubular volume and hypocellular glomeruli with small surface area. After birth the cuboidal glomerular epithelium is replaced by specialized epithelial cells. The tubules lengthen and absorption and secretion increase while the tubular volume attains maturity earlier than the glomeruli.

Glomerular filtration rates (GFR) decrease in the first 24-48 hours, but rise again by the 7th-10th day. In the first month of life the mean GFR is about 25-33% of that expected for size as related to adult values. Between 3 and 6 months of age it is 50%, rising to 75% between 6 and 12 months of age. About the middle of the second year of life the GFR becomes 100% of the expected figure of size. The concentration capacity at birth is also immature. The infant's kidney can concentrate urine to a maximum of about 700-800 mmol/kg whereas the older child and adult can achieve 1200-1400 mmol/kg (Houston, Oetliker, 1981; Smith and Smith, 1982; Hatch, Sumner, 1986).

The half-life of a drug, excreted unchanged through the kidneys is often inversely correlated to the gestational age. This is most probably connected to the inverse correlation between glomerular filtration rate and gestational age. After the first 3-5 days of life, especially in full term babies, usually a significant reduction in plasma half-life occurs of those drugs, excreted mainly through the kidneys. The capacity of neonates to metabolise drugs shows a large interindividual variability.

Renal elimination accounts for 40-50% of the clearance of d-tubocurarine and pancuronium, thus renal failure has a profound effect on their pharmacokinetics. The clearance is decreased so the terminal elimination half-life is increased. With small doses the effect is minor, but with larger paralyzing doses the recovery rate of paralysis is delayed. Approximately 12% of d-tubocurarine is normally eliminated unchanged into the bile, but if the renal elimination is impaired this percentage increases. For pancuronium the situation in renal failure is more adverse as its active metabolites are also normally excreted by the kidney (Stanski, Watkins, 1982). Atracurium is spontaneously broken down by Hofmann elimination to inactive breakdown products. Vecuronium elimination is not dependant on renal clearance. Both drugs are suitable muscle relaxants for patients without renal function. Thus considering the immature renal function of the neonate, d-tubocurarine and pancuronium should be avoided whereas atracurium and vecuronium can safely be used.

MATURATION OF THE LIVER

Before birth most of the functions of the liver are performed by the placenta or by the maternal liver, but at birth the liver must take on its role in body homeostasis. The weight of the liver is 4% of total body weight in the newborn, compared to 2% in the adult.
At birth there is great diversity in the maturation of enzyme systems. Some aspects of liver function such as detoxication and carbohydrate metabolism are poorly developed, with resultant inability to metabolize such compounds as bilirubin and chloramphenicol for several weeks after birth. The O-dealkylation of pancuronium and vecuronium is less

affected. Other functions such as synthesis of albumin and coagulation factors are relatively normal. Because of this impaired metabolism almost all of the drugs studied in the neonatal period have a prolonged elimination half-life. Pathologic conditions such as hypoxemia, cardiac failure and poor nutritional status may further depress the activity of metabolizing enzymes in the newborn. The ability to metabolize drugs can be enhanced by maternal exposure to enzyme inducers, such as smoking and phenobarbitone (Sereni et al., 1981). Maturation of liver enzyme systems occurs rapidly. Usually by 3 months of age the enzyme systems function at adult level. The initial phase of reduced metabolic clearance in the neonate is followed by a phase of marked increase in metabolic activity in the infant and child. The period in which this occurs is highly variable and unpredictable, but comes after improvement of the clearance of unchanged drugs through the kidneys. The faster recovery in children, compared to adults, from twitch paralysis by some relaxant drugs can be explained on the basis of enhanced hepatic excretion of metabolic clearance. This has been demonstrated for pancuronium and vecuronium, muscle relaxants with a high liver clearance. For d-tubocurarine, excreted unmetabolized by the kidney, this was not confirmed (Martyn, 1986).

CHANGES IN BODY COMPOSITION

The total body water content of the newborn is proportionately higher than the adult, due principally to a relative excess of extracellular fluid. Neonates at term consist for 82% of the fat-free weight of water and adults for 72%. Extracellular water in premature infants is about 50% of the body weight, decreasing to 45% at term, 30% at two months of age, 23% at adolescence and 16% in adults.
The intracellular fluid increases from 30% in prematures to 35% of the body weight at birth, to 40% at the age of one year and to 47% at 7-16 years.

The percentage of fat in the body falls considerably between 1 and 5 years of age. Thereafter it increases, more in females than in males. But in adipose tissue it increases from 45% at birth to 60% at 6 months of age. Skeletal muscle, in relation to body composition, is

quantitatively the most important soft tissue. It accounts for 25% of the body weight of the preterm and full term baby and 40% of the weight of an adult (Widdowson, 1981).

The difference in body composition and metabolism of immature tissues must be considered as the physiological basis for the differences in drug disposition in newborn and premature infants compared with older children and adults. The distribution volume of a drug is mainly determined by the amount of body water and the degree of binding to plasma-proteins, the size of fat depots and tissue binding. In neonates the total body water and the extracellular water as a percentage of body weight are high. Fat depots are relatively small and the total amount of muscle tissue is low. All these factors can influence the relative volume of distribution (RVD). In the majority of the cases the RVD is found to be greater in neonates. The primary cause of this is the relatively greater extracellular water volume and possibly some difference in the plasma protein binding of the drugs. The molecular mechanisms underlying reduced plasma protein binding in newborn infants are not yet entirely understood. But the concentration in those tissues for which the drug is active still determines the therapeutic effectiveness (Sereni et al., 1981).

Nondepolarizing muscle relaxants are highly ionized, regardless of pH, extremely water soluble and unable to penetrate cell membranes rapidly. Distribution of these drugs is limited to extracellular water (Stanski, Watkins, 1982). Since the percentage of bodyweight of extracellular water is higher in neonates the final drug concentration is lower when the given dose of relaxant is based on body weight. The distribution volume is increased in neonates as demonstrated for d-tubocurarine (Fisher et al., 1982).

CLINICAL EXPERIENCES WITH NONDEPOLARIZING RELAXANTS IN PAEDIATRIC ANAESTHESIA

In 1950 G. Jackson Rees stated in his article "Anaesthesia in the newborn", that "the time has come to consider the problem of anaesthetizing the newborns in relation to their peculiar physiology". He proposed that control of respiration is extremely desirable in

infants, but the use of relaxant drugs in neonatal anaesthesia was contra- indicated, being unnecessary (Jackson Rees, 1950). In the years to follow however, muscle relaxants became a part of anaesthetic technique for operations on newborn infants. Stead wrote in 1955 that in Liverpool over three hundred neonatal surgery cases have been performed using relaxants. He used an ingenious device to measure respiration pressure using suxamethonium chloride and d-tubocurarine chloride as relaxants. He concluded that resistance of the neonate to the depolarizing agent suxamethonium chloride is clearly shown, but that neonates are extremely sensitive to the competitive blocking agent d-tubocurarine chloride. In this regard they resemble a myasthenic patient (Stead, 1955).

Salanitre described the respiratory complications associated with the use of muscle relaxants in young infants. He reviewed 220 infants less than 13 weeks of age (Salanitre, 1961). He found that 27% of the infants given a muscle relaxant had postoperative respiratory depression, compared to 12% in those who did not receive any relaxant. This increase in respiratory depression rate was partly due to the hypothermia that occurred more often if the patient was relaxed and partly as a result of overdose of the relaxant. Although Churchill-Davidson and Wise found in the first few weeks of life a neonate to resemble a myasthenic patient, they failed to show an increased sensitivity of the hypothenar muscles to d-tubocurarine under cyclopropane anaesthesia using EMG (Churchill-Davidson, Wise, 1963).

Lim used a dose of d-tubocurarine to produca respiratory depression without apnea in 134 children from 5 weeks to 16 years of age and found that children under 1 year of age required about one-fourth of the dose per kg compared to children over 12 years of age (Lim et al., 1964). Long urged caution in the use of d-tubocurarine in infants and children. He stated that provided small initial doses are used, body cooling is avoided, no deep halothane anaesthesia is given and as a routine drugs are used for reversal, no special hazards exist with the use of d-tubocurarine in halothane anaesthesia, measuring the hypothenar EMG response (Long, Bachman, 1967). Two years later Walts and Dillon found newborns to be more sensitive to d-tubocurarine than

adults, when administered on the basis of surface area using halothane and force of thumb adduction (Walts, Dillon, 1969).

In the 1970's confusion had not lessened. Bennett and colleagues studied pancuronium and d-tubocurarine in many children including neonates. They seldom used a nerve stimulator, thus seldom measured EMG or MMG. Clinical signs were their guideline for determining onset time and recovery. They found that the onset time of pancuronium increases with age and the duration of action with increasing doses. A special observation was made, when they reported the potency ratio of pancuronium, compared to d-tubocurarine, to range from 9:1 at birth to 6:1 at one month of age (Bennett et al., 1975). Bennett and colleagues also studied the effect of tubocurarine in 50 neonates (1-28 days) including 27 born prematurely. They found that tubocurarine, given in a bolus can be used safely. The recommended dose doubles from 250 mcg/kg at birth to 500 mcg/kg at 28 days. This dose must be reduced in the event of prematurity, acidosis or hypothermia, or when certain antibiotics or inhalation anaesthetic agents are present in the tissues. Reversal can be obtained after one hour (Bennett et al., 1976).

Lippman and Rogoff failed to show a benefit for calculating doses on basis of surface area rather than on the basis of weight in a study of 100 children (1-10 years of age). They used a nerve stimulator on the ulnar nerve but estimated the muscle response in an unclear way. The children were divided in 5 age groups regarding onset time, but results are practically uniform. The duration of action is not given for different age groups (Lippman, Rogoff, 1974).

Goudsouzian and coworkers were the first to attempt to draw an accurate dose-response curve of pancuronium in the paediatric age group. They studied the force of the thumb resulting from single stimulations of the ulnar nerve. Incremental doses were given to 17 patients (5 weeks to 7 years old) including 3 infants from 5, 7 and 7 weeks old, all under halothane anaesthesia. The 3 small infants did not show a different dose-response curve when compared with older children, but dosage based on surface area is excessive for infants. No division in age groups was made. Comparing their study with others

they came to the conclusion that children may require more pancuronium than adults to reach the same degree of muscle relaxation. Recovery rate however is the same as in adults (Goudsouzian et al., 1974). One year later another study from Goudsouzian and colleagues was published. This time on d-tubocurarine in 44 children of 4 different age groups (1 day-7 years old), using basically the same technique as in 1974. The cumulative dose-response curves showed a tendency of the infant of 1 day old to require higher doses of d-tubocurarine to achieve the same amount of twitch inhibition as their older confreres. The same age group showed the widest deviation of response. However a statistically significant difference was not found in dose-response using single twitches nor in recovery time using train-of-four in the various groups of infants and children in this study. However infants and children seem to recover somewhat faster than adults from similar levels of neuromuscular depression produced by d-tubocurarine. In the same study a high correlation (r=0.93) is shown between single twitch and train-of-four (Goudsouzian et al., 1975).

Antagonism of blockade

For the reversal of residual neuromuscular blockade cholinesterase drugs are used. Inadequate reversal is likely to occur if it is attempted within 30 minutes of the time of administration of the relaxant or if potent anaesthetic agents are used as part of the anaesthetic technique (Bennet et al., 1971).

PHARMACOKINETICS AND PHARMACODYNAMICS OF d-TUBOCURARINE AND PANCURONIUM

d-Tubocurarine (fig. 4)

A combined pharmacokinetic and pharmacodynamic study in 9 children (1 month-9 years old) showed that plasma levels of d-tubocurarine at steady state 50% depression of twitch height [$Cp_{ss(50)}$] are not different between children and adults. Neither are there differences in the central and steady state volumes of distribution and distribution half-lives between children and adults. However the clearance is greater and the elimination half-life correspondingly shorter in

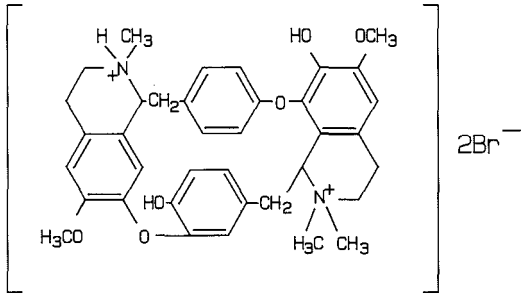


Fig. 4 d-Tubocurarine

children. Anaesthesia was induced and maintained with halothane. Paralysis was assessed by quantitating the electromyographic twitch height in reponse to supramaximal stimulation of the ulnar nerve (O'Keeffe et al., 1979).

In 1982 an article on pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children and adults was published by Fisher and colleagues 31 patients were studied, divided in neonates (0-2 months old), infants (2-12 months old), children (1-12 years old) and adults. All patients received 0.58 MAC halothane. Single supramaximal stimuli were given to the ulnar nerve and the resulting EMG of the adductor pollicis muscle was measured. d-Tubocurarine concentrations were measured and fitted in a two-compartment, first-order pharmacokinetic model. The plasma d-tubocurarine concentration at which 50% depression of EMG twitch height occurred [$Cp_{ss(50)}$] was found significantly lower in neonates and infants than in children and adults. The steady state distribution volume (Vd_{ss}) in neonates is greater and the elimination half-life longer than in children and adults. The authors concluded to an increased sensitivity to d-tubocurarine as determined by $Cp_{ss(50)}$. However because of the larger Vd_{ss} in younger patients, dose size does not differ with age. In addition, because of the longer elimination half-life in neonates, second and subsequent doses are required at less frequent intervals (Fisher et al., 1982).

Matteo and coworkers studied the distribution and urinary excretion of d-tubucurarine over a period of 24 hours and in some of the 35 patients they also measured the EMG in hopes to reconcile conflicting

reports. The EMG was recorded after single stimuli of the ulnar nerve during halothane anaesthesia. Patients were divided in neonates (0-1 month old), infants (1-12 months old), children (1-4 years old) and adults. No differences were found between the initial volume of distribution. Both neonates and infants exhibit decreased plasma clearance and a prolonged half-life of elimination. The neonate's 24 hours urinary excretion is significantly less than the adult volume. The plasma concentration - EMG response between 20 to 80% paralysis did not show a difference between the age groups except for 2 of the 7 measured neonates. They were found to be less sensitive to d-tubocurarine and were placed in a subgroup. The recovery did not show a difference between the various age groups (Matteo et al., 1984).

Pancuronium (fig. 5)

An electromyographic study using train-of-four on pancuronium in 14 children (6 months-12 years old) under light halothane anaesthesia (less than 0.5%) revealed no differences in duration and degree of blockade from pancuronium between an age group of 0.5-6 years old and an age group 7-12 years old. Train-of-four ratio is found to be more sensitive than single twitch as an index of the recovery of transmission (Esener, 1983).

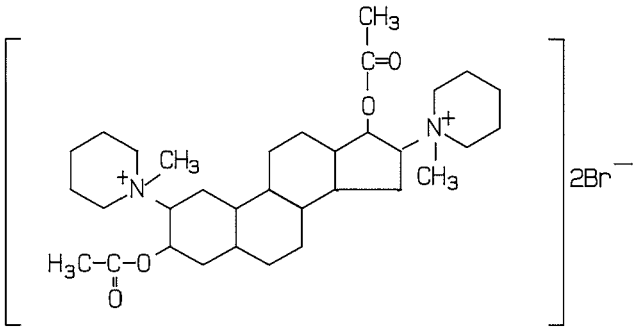


Fig. 5 Pancuronium bromide

Comparative studies on d-tubocurarine and pancuronium

The relation between train-of-four ratio and single twitch after

d-tubocurarine and after pancuronium was further studied by Robbins and colleagues in 40 patients, aged from 1 day-12 months.
The force of contraction of the adductor pollicis muscle after stimulation of the ulnar nerve was measured under narcotic anaesthesia. The decrease in force of contraction in response to a single stimulus compared with control, was indicative of the classical postjunctional site of action. A fade of response to train-of-four stimulation occurred. They found more prejunctional effects during the recovery phase than during onset for d-tubocurarine and pancuronium, the prejunctional effects being more marked with d-tubocurarine. But prejunctional neuromuscular activity is less marked in infants than in adults (Robbins et al., 1984).

Goudsouzian and coworkers in a comparative study between d-tubocurarine and pancuronium found, that the duration of action is shorter in children (4 months-10 years of age) than in adults. They used the force of thumb adduction after train-of-four stimulation of the ulnar nerve under narcotic anaesthesia (Goudsouzian et al., 1981). In 1984 the same group compared identical muscle relaxants in 56 children (1-15 years old). They determined the cumulative dose-response curves under narcotic anaesthesia with single stimulation of the thumb and recorded the force of thumb adduction. They found that children have a tendency to require more relaxant and to recover more quickly than adults. But a statistical significance was not proven (Goudsouzian et al., 1984).

PHARMACOKINETICS AND PHARMACODYNAMICS OF ATRACURIUM AND VECURONIUM

In the 1980's the nondepolarizing muscle relaxants atracurium and vecuronium were introduced in clinical anaesthesia. Considering the sensitivity of the neonate and the prolonged recovery phase of relaxation in the newborn, these relaxants of intermediate duration are very welcome.

Atracurium (fig. 6)

The pharmacokinetics of atracurium in infants (1-8 months of age)

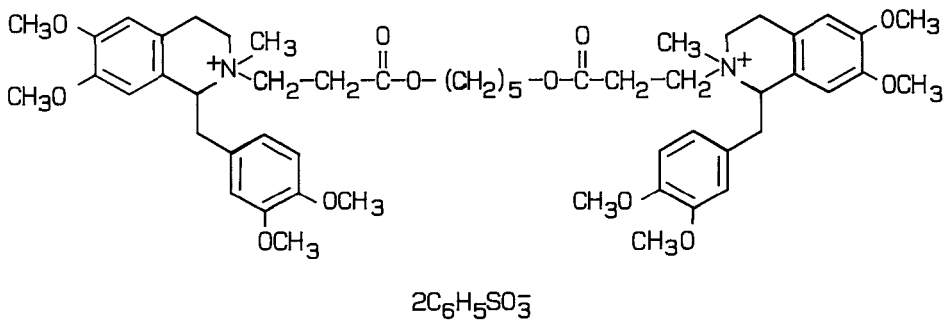


Fig. 6 Atracurium besylate

and children (2-10 years of age) have been studied by Brandom and coworkers during isoflurane anaesthesia. They found a significant difference in volume of distribution (ml/kg) and clearance of atracurium (ml/kg/min).
Infants show a larger volume of distribution and a higher clearance. Plasma elimination half-lives (T 1/2 alpha and T 1/2 beta) and the clearance expressed on a basis of body surface (ml/m^2/min) tend to be shorter in infants as compared to children, but these trends did not reach statistical significance (Brandom et al., 1986).

Some investigators measured the infusion rate, necessary to obtain a steady state blockade of a certain percentage, reflecting the rate of removal. Brandom and colleagues adjusted the infusion rate of atracurium to maintain neuromuscular block within the range of 89-99% using EMG and first twitch to control in children of 2-10 years. During fentanyl anaesthesia the infusion rate was 558 mcg/kg/h (13560 mcg/m^2/h), during 0.8% halothane anaesthesia 408 mcg/kg/h (10500 mcg/m^2/h), and during 1% isoflurane anaesthesia 354 mcg/kg/h (8820 mcg/m^2/h) (Brandom et al., 1985).

Goudsouzian studied atracurium in children aged 1-10 years, maintaining a blockade of 90-99% of control, using MMG and first twitch compared to control. During morphine anaesthesia the infusion rate was 558 mcg/kg/h, during 1% halothane 498 mcg/kg/h and with 2% enflurane 294 mcg/kg/h (Goudsouzian et al., 1986a). In another report from Meretoja and Kalli (1986a), no halogenated anaesthetic agents were used. Two groups were studied with fentanyl anaesthesia, using EMG and

train-of-four stimulation. Newborn infants to 3 months of age required a continous infusion of 400 mcg/kg/h and children over 5 kg to 16 years of age 530 mcg/kg/h.

Gramstad and Lilleaasen (1985) studied adults, using fentanyl anaesthesia, MMG and first twitch compared to control. For atracurium the infusion rate to maintain 90% blockade had to be set at 383 mcg/kg/h. Eagar and collegues (1984) studied atracurium in patients from 42-77 years old under halothane anaesthesia (0.25-0.5%), using MMG and first twitch. They found a requirement of 366 mcg/kg/h to maintain a blockade of 90-100%. D'Hollander and coworkers (1982) found 2791 mcg/m^2/h and Noeldge and colleagues (1984) 87 mcg/kg/h, both using MMG and fentanyl anaesthesia. Brandom and colleagues (1985) compared their results with the results of D'Hollander and coworkers (1982), who studied three adult age groups. They concluded that when infusion requirements are expressed on a surface area basis, the rate of removal of atracurium is independent on age from 2-85 years of age.

The clinical effect of atracurium in 270 neonates was observed by Nightingale. He advised a lower dose of atracurium (300 mcg/kg instead of 500 mcg/kg) in neonates less than 48 hours old, especially when body temperature is low (less than 36°C). The reason for this being an increased recovery time (Nightingale, 1986). Cook found older children (24 boys, median age 13 years) to be somewhat resistant to atracurium compared to adults. He measured the thenar EMG with train-of-four stimulation of the ulnar nerve during halothane anaesthesia. He also warned that when using a cumulative dose-response curve instead of a single dose method one overestimates the ED_{95} by 55%. The ED_{95} estimated from the single dose response curve is 154 mcg/kg and the ED_{50} is 101 mcg/kg (Cook et al., 1982). In 1986 Cook and coworkers found age-related differences using the same method, between 45 infants (age 1-6 months) and 45 children (age 2-10 years) in ED_{50} and ED_{95} for atracurium but not for pancuronium. Unfortunately numbers are not given (Cook et al., 1986).

Meretoja and Kalli studied the effects of a bolus dose of 0.4 mg/kg atracurium under balanced anaesthesia, measuring single twitch and train-of-four ratio quantified by EMG of the hypothenar muscles. They found the control value of the train-of-four ratio to be 99 ± 1% in

patients under 5 kg body weight as compared to 100% in heavier patients. The maximal blockade in 65% of the patients under 10 kg was more than 98% whereas this was only 32% in patients over 10 kg. The recovery rate (75-25% EMG depression) is longer in patients under 5 kg than in patients from 5-10 kg and longer in patients from 5-10 kg than in heavier patients (14.2, 11.6 and 10.2 min respectively) (Meretoja, Kalli, 1986b).

Another comparison of atracurium-induced neuromuscular blockade in neonates, infants and children was made by Meakin and colleagues under balanced anaesthesia, measuring force of thumb adduction after single twitch stimulation. Neonates (1-28 days old) appeared to be more sensitive to atracurium than infants (1 month-1 year old) and children (1-5 years old). The ED_{50}'s are respectively 79 mcg/kg,115 mcg/kg and 137 mcg/kg. The ED_{95}'s are respectively 109 mcg/kg, 155 mcg/kg and 191 mcg/kg. However the recovery of the first twitch to 10% of the control is significantly faster after a bolus of 0.5 mg/kg atracurium in neonates (22.1 min) than in infants (29.7 min) and children (28.6 min) (Meakin et al., 1987).

Brandom and coworkers performed many studies on atracurium in infants from 1 month old to children of 10 years of age. Infants (1-6 months old), children (2-10 years old) and adolescents (11-16 years old) were given atracurium under halothane (1% end tidal) anaesthesia. The ulnar nerve was stimulated by train-of-four and the resulting EMG of the thumb was recorded. The percentage block was calculated by comparing the first twitch to the control measurement. Dose-response curves were calculated from single doses. ED_{50} and ED_{95} were calculated on a base of weight and of body surface area. For neonates the ED_{50}'s are 85 mcg/kg and 1600 mcg/m^2, for children 132 mcg/kg and 3266 mcg/m^2 and for adolescents 101 mcg/kg and 3338 mcg/m^2. The ED_{95}'s are for neonates 156 mcg/kg and 3330 mcg/m^2, for children 260 mcg/kg and 6628 mcg/m^2 and for adolescents 157 mcg/kg and 6302 mcg/m^2. The dose-response curve for children is shifted significantly to the right, compared to infants and adolescents, when calculated on a weight base. However when calculations were made on surface area basis the dose-response curves for children and adolescents were identical and the curve for infants shifted significantly to the left of the

other two groups. Brandom and coworkers also found halothane to potentiate the effect of atracurium but no significant difference was found. Recovery time after equal multiples of the ED_{95} was significantly shorter in infants than in older children and adolescents, but the recovery time from 25 to 95% of control does not differ between the three age groups (Brandom et al., 1984).

A comparison of the pharmacodynamic data on atracurium was made by Goudsouzian studying infants (4 weeks-1 year old), children (1-10 years old) and adolescents (11-17 years old) under halothane anaesthesia. Train-of-four stimulation of the ulnar nerve was used and the resulting force of thumb adduction measured. The percentage of blockade was the first twitch related to the control. The time from injection to maximal effect and the recovery time were not different between the age groups. However a significantly faster recovery time was observed in children as compared to adults, both groups during narcotic anaesthesia. Cumulative dose-response curves with halothane anaesthesia were made for each age group. The calculated ED_{50} and ED_{95} did not show a difference when expressed in mg/kg, (ED_{50} 0.10, 0.11 and 0.12 mg/kg and ED_{95} 0.17, 0.17 and 0.18 mg/kg). But calculated on surface area infants are more sensitive to atracurium than children and children more than adolescents: respectively ED_{95} 3.3, 4.7 and 6.4 mg/m^2 (Goudsouzian et al., 1985). A significant difference in ED_{50} and ED_{95} of infants of 1-3 months of age and infants of 3-12 months of age was found by Meistelman and colleagues. But they found this difference both when calculated on weight and on surface area basis. The calculated ED_{50}'s are respectively 86 mcg/kg equals 1408 mcg/m^2 and 131 mcg/kg equals 2664 mcg/m^2. The ED_{95}'s are 175 mcg/kg equals 3281 mcg/m^2 and 205 mcg/kg equals 4544 mcg/m^2. The technique used by this group was stimulation of the ulnar nerve and measuring the EMG of the thenar muscles under halothane anaesthesia (1 MAC) (Meistelman et al., 1986a).

Vecuronium

As vecuronium is the subject of our study, it is discussed separately in Chapter III. The last part of that chapter describes the

pharmacokinetics and pharmacodynamics of vecuronium in the paediatric age group.

GENERAL CONCLUSIONS

Comparing studies on non-depolarizing neuromuscular blocking agents in adults is difficult (Miller, 1986). Factors such as stimulation technique and choice of monitoring technique of the evoked responses of the muscle are important. Major artefacts can be caused by interactions with other drugs used, including anaesthetics and depolarizing blocking agents (Viby-Mogensen, 1985), by changes in body temperature and by acid-base balance. All this is also of concern in studies on the paediatric age group. In this group however growth and development are also major factors. Body composition changes and liver, kidney and neuromuscular junction become mature. It is thus not surprising that much confusion exists. There is little measure of agreement between various authors, neither in their ways of experimental procedure, nor in their conclusions. Between the ages of 0 and 1 year it is not possible to compare various studies as no two age groups for children are identical and anaesthesia and monitoring technique also vary. For vecuronium only two studies have been performed in infants, both using halothane anaesthesia but with different monitoring techniques.

Since little is known about the pharmacodynamics of vecuronium in the paediatric age group, especially in infants, and since vecuronium is a modern relaxant of intermediate duration best meeting the concept of an ideal muscle relaxant (Booij, Crul, 1983), the aim of this study is to investigate pharmacodynamics in neonates, infants and children. Using a uniform procedure and keeping all variables as normal as possible within each age group enables a comparison to be made between neonates, infants and children.

III VECURONIUM BROMIDE

The first to describe the synthesis and pharmacology of vecuronium bromide, which was then still known as ORG NC 45, were Buckett, Hewett and Savage (1973). In search of the ideal neuromuscular blocking drug (Karis, Gissen, 1971; Savarese, Kitz, 1973) research was being done on derivates of steroidal relaxants and the bulky choline esters. Thus the pavulon analogues were investigated by (in alphabetical order) Agoston, Booij, Bowman, Crul, Marshall, Miller and their coworkers. All these compounds have in common the androstane skeleton (fig. 7).

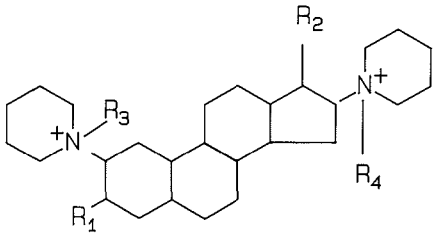


Fig. 7 Androstane skeleton

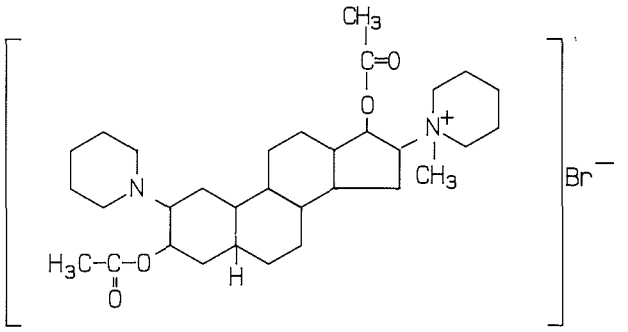


Fig. 8 Vecuronium bromide

The investigated compounds differ only in the side chains at the C3, C17 and the two N-atoms (Booij, 1982). Org NC 45 (fig. 8) is the most

potent of the monoquaternary compounds. Its structural formula is: 1[(2 beta, 3 alpha, 5 alpha, 16 beta, 17 beta) - 3, 17 - bis (acetyloxy) - 2 - (1-piperidinyl) - androstan - 16 - YL] - 1 - methylpiperidinium bromide.

Marshall (1968) found the block produced by ORG NC 45 to be of a nondepolarizing type. With the knowledge available at that time no advantages were seen with this compound. Moreover the compound is unstable in aqueous solution (Savage et al., 1980) and further investigations were temporarily abandoned.

The importance of cardiovascular side effects of neuromuscular blocking drugs gradually became more apparent. Accordingly a series of analogues of pancuronium was tested again (Savage et al., 1980). ORG NC 45 again became a subject of research. Animal investigations began in 1975 (Durant et al., 1979a; Marshall et al., 1980), followed by the first human studies (Crul, Booij, 1980; Baird, Herd, 1980; Buzello et al., 1980; Krieg, Crul et al., 1980; Van der Veen, Becini, 1980).

Animal studies confirmed that the block caused by ORG NC 45 is of a nondepolarizing nature and mainly postjunctional in origin (Durant, et al., 1979a; Torda, Kiloh, 1982). Vecuronium is a highly potent neuromuscular blocking drug in the same order as pancuronium (Kerr, Baird, 1982; Agoston et al., 1980; Gramstad et al., 1982). The approximate relative potency of vecuronium in adult man based on calculations of the effective vecuronium dose resulting in a maximal blockade of 50% (ED_{50}) as compared with d-tubocurarine is 5.6. For pancuronium this is 4.7 and for atracurium 1.1. The ED_{50} of vecuronium varies in different studies on adults between 15 and 31 mcg/kg as an i.v. bolus dose. The ED_{90} lies between 23 and 43 mcg/kg and the ED_{95} between 38 and 56 mcg/kg. A major cause of the differences found here is the variation in techniques (Fahey et al., 1981a; Gramstad et al., 1983; Robertson et al., 1983a; Engbaek et al., 1984; O'Hara,1985). Vecuronium has a sufficiently high affinity for the recognition sites of the postjunctional receptors for it to block transmission before any ion channel occlusion is produced (Baird et al., 1982). The latter is difficult to reverse with anticholinesterase agents. Vecuronium blocks the postulated prejunctional receptors and so produces the various fade phenomena on train-of-four and tetanic stimulation

(Bowman, Webb, 1976; Bowman, 1980a; Bowman et al., 1983; Williams et al., 1980; Baker, 1986).

Pharmacodynamically vecuronium is a nondepolarizing neuromuscular blocking agent with an intermediate duration of action. The clinical duration of muscle relaxation (time between injection and return of twitch to 25% of control) is 21-38 minutes in adults (Agoston, 1983; Foldes et al., 1983; Bencini, Newton, 1984; Engbaek et al., 1984). A dose of vecuronium producing 90% depression of contraction results a total duration of action (time from injection to 90% recovery) of ca. 25 minutes in adults. A bolus dose varying from 20-100 mcg/kg has a duration of action of 20-45 minutes (Agoston et al., 1980; Fahey et al., 1981a; Ali et al., 1983; Booij, Crul, 1983; Engbaek et al., 1983a). Thus vecuronium in adults has the shortest duration of action of all clinically used nondepolarizing muscle relaxants. In adults the recovery rate (time from 25-75% recovery) after a bolus injection of vecuronium 43-120 mcg/kg varies from 6.8-15 minutes (Agoston et al., 1980; Ali et al., 1983; Robertson et al., 1983a; Bencini, Newton, 1984).

Using comparable doses of relaxant the recovery rate of vecuronium is the shortest (10 minutes) directly followed by atracurium (11 minutes). The recovery rate of pancuronium is long (32 minutes) and of d-tubocurarine the longest (59 minutes).

Unfortunately the rapid onset time (time from injection to maximal effect) of suxamethonium chloride, a depolarizing relaxant drug is unequalled by any nondepolarizing relaxant. But the onset times of vecuronium and atracurium are shorter than the onset times of most other nondepolarizing relaxant drugs. After a bolus injection of vecuronium 73-200 mcg/kg onset times varying from 2.2-6.7 minutes were measured in adults (Agoston et al., 1980; Fahey et al., 1981a; Gramstad et al., 1982a; Foldes et al., 1983; Bencini, Newton, 1984; Engbaek et al., 1984). Little or no cumulation at all is found for vecuronium (Agoston et al., 1980; Fahey et al., 1981a; Buzello, Nöldge, 1982; Ali et al., 1983; Engbaek et al., 1984; Fisher, Rosen, 1986). The reversibility of vecuronium by cholinesterase inhibitors equals that of pancuronium (Baird et al., 1982; Gencarelli, Miller, 1982; Caldwell et al., 1986).

Animal studies show a lack of cardioselective atropine-like action of vecuronium at clinical blocking doses and at doses many times greater (Durant et al., 1979a; Booij et al., 1980a; Marshall et al., 1980; Marshall et al., 1983). In human studies vecuronium is without sympathetic stimulation, ganglion blockade or vagolytic effect (Crul, Booij, 1980; Krieg et al., 1980a; Agoston et al., 1980; Fahey et al., 1981a; Barnes et al., 1982; Engbaek et al., 1983b; Morris et al., 1983; Cozanitis, 1986). Histamine release as seen with the use of d-tubocurarine and to a lesser extent with atracurium is of no concern in the case of vecuronium (Booij et al., 1980b; Basta et al., 1983; Robertson et al., 1983b).

Pharmacokinetically vecuronium is characterised by a rapid total plasma clearance (Sohn et al., 1982; Cronnelly et al., 1983). This is mainly due to substantial hepatic uptake shortly after intravenous injection. For a large proportion no further redistribution takes place. Total biliary elimination amounts to 40-50% of the administered dose. Renal excretion is 20-30% of the injected vecuronium, the majority of which is eliminated within 12 hours after administration. Most of the vecuronium is unchanged (Bencini et al., 1983). Less than one-fifth of the total amount is eliminated as the 3-OH metabolite and this breakdown product has not been detected in plasma (Sohn et al., 1982). Plasma concentration data do not show statistically significant differences in patients with no renal function compared to healthy subjects. In these renal failure patients, even with extremely large doses, the duration of neuromuscular blockade was unchanged (Fahey et al., 1981b; Bencini et al., 1983; Meistelman et al., 1983; Hunter et al., 1984). This is in contrast to the duration of blockade in patients with liver disease, who displayed a prolonged effect of vecuronium, which is more pronounced in cirrhosis than with cholestasis (Duvaldestin et al., 1982, 1983; Lebrault et al., 1986).

PHARMACOKINETICS AND PHARMACODYNAMICS OF VECURONIUM IN THE PAEDIATRIC AGE GROUP

A pharmacokinetic study on 5 infants (3-11 months) and 5 children (1-5 years old) using a 3-compartment model showed a larger volume of

distribution at steady state (Vd_{SS}) and a larger mean residence time (MRT=Vd_{SS}/Cl, where Cl=total plasma clearance) in infants compared to children. The estimated steady-state plasma concentration that results in 50% depression of twitch tension (force-of-thumb adduction), $Cp_{SS(50)}$ is lower in infants. All other pharmacokinetic parameters do not change with age. These results are similar to the age-related changes for d-tubocurarine (Fisher et al., 1982, 1985a,b).

Meistelman and coworkers published a pharmacokinetic study on vecuronium in anaesthetized children. They studied vecuronium and pancuronium in 12 children of 3-8 years old under halothane (1 MAC) anaesthesia, using single twitch stimulation of the ulnar nerve and recording the resultant EMG of the thumb. A bolus of 0.1 mg/kg was given. The plasma clearance (Cl) and the volume of distribution at steady state (Vd_{SS}) are significantly greater in vecuronium than in pancuronium (Cl_{vec} 2.8 and Cl_{pan} 1.7 ml/kg/min; Vd_{ssvec} 320 and $_{pan}$ 203 ml/kg).

No significant difference was found in the plasma concentration of either drug measured at 50 and 90% recovery, nor in the elimination half-life (Meistelman et al., 1985). Continuous infusion studies on vecuronium have only been made in adults (D'Hollander et al., 1982; Noeldge et al., 1984; Gramstad, Lilleaasen, 1985).

Vecuronium in paediatric anaesthesia has been studied by several investigators. Unfortunately all these studies were conducted under halothane anaesthesia. Although not as strongly potentiating as enflurane and isoflurane, halothane has a dose-dependent influence on the action of vecuronium (Leuwer, Dudziak, 1986). It remains unknown as to what dosages should be used in different age groups to cause equal effects on the neuromuscular system.

Goudsouzian and colleagues stimulated the ulnar nerve with a train-of-four and measured the evoked thumb adduction. A cumulative dose-response curve was calculated for 40 children (2-9 years old) and adolescents (10-17 years old). Children were found to be significantly more resistant to the neuromuscular effect of vecuronium than adolescents. For children, respectively adolescents, the ED_{50} is 33 mcg/kg, 23 mcg/kg, the ED_{90} 51 mcg/kg, 39 mcg/kg and the ED_{95} 60 mcg/kg, 45 mcg/kg. The time from injection to maximal effect and the

time to full recovery of the first twitch compared to control do not show a statistically significant difference between the two age groups. The correlation between the MMG twitch height (T 1% of control) and train-of-four ratio values for vecuronium is found to be linear ($r=0.91$; $p < 0.001$) (Goudsouzian et al., 1983b).

Histamine release, which may be of concern in the use of atracurium, is of no importance in vecuronium. The onset times of both drugs are comparable but the recovery of a bolus dose of 120 mcg/kg vecuronium from maximal twitch depression (T1) to 95% recovery is slightly shorter than of a bolus dose of 600 mcg/kg atracurium (atracurium 58.7 min, vecuronium 44.6 min) (Goudsouzian et al., 1986b,c).

Pharmacodynamics of vecuronium were studied by Fisher and coworkers in 24 infants (age 7-45 weeks), 24 children (age 1-8 years) and 6 adults (age 18-38 years) under halothane anaesthesia (0.9 MAC) with single twitches of the ulnar nerve, recording electromyogram and mechanomyogram of the thumb. Onset time (injection-peak effect) does not show a statistically significant difference between infants (1.5 min) and children (2.4 min). However the onset is significantly more rapid in infants than in adults (2.9 min). The duration (injection-90% recovery of MMG) is significantly faster in infants (73 min) than in children (35 min) but not significantly faster than in adults (53 min). Recovery rate (25-75% recovery) showes the same (infants 20 min, children 9 min and adults 13 min). The potency between the three age groups does not differ significantly (ED_{50} infants 16.5 mcg/kg, children 19.0 mcg/kg and adults 15.0 mcg/kg). A good correlation is found for each age group between EMG and MMG ($r=0.92$) (Fisher, Miller, 1983). Schwartz and colleagues (1985) studied one group of children (1-10 years of age) during halothane anaesthesia with EMG and MMG They found the ED_{50} of vecuronium 22.4 mcg/kg and the ED_{90} 36.8 mcg/kg. Motsch and coworkers measured onset and recovery of vecuronium induced neuromuscular blockade in 21 infants (age 1 day-10 months) and 21 children (age 1-6 years) under halothane anaesthesia (max. 1 vol. %). They found a significantly shorter onset time (injection-max. effect) and a longer duration and recovery rate in infants as compared to children. For infants, respectively children, the onset time is 1.4 min and 2.7 min, the duration (injection-25% recovery) 25 min and 18

min and the recovery rate (25-75%) 18 min and 10 min (Motsch et al., 1985).

A comparison between vecuronium and pancuronium in children (3-8 years of age) was made by Meistelman and coworkers. Recovery is significantly faster in vecuronium. The duration of action (time from injection-90% recovery of T1) is 35 min for vecuronium and 92 min for pancuronium. And the recovery rate (25-75% recovery) for vecuronium is 7 min and for pancuronium 28 min (Meistelman et al., 1985). In a similar study on 14 children of 4-8 years, using 1% halothane a bolus of 0.1 mg/kg vecuronium had an onset time of 3.1 min, a duration of action of 36.5 min and a recovery rate of 9.3 min. A calculated dose-response curve of 33 children of the same age shows an estimated ED_{50} 31 mcg/kg, ED_{90} 55 mcg/kg and ED_{95} 64 mcg/kg (Meistelman et al., 1986b).

Vecuronium exhibits most of the proporties of the ideal neuromuscular blocking drug. Of the nondepolarizing blocking drugs atracurium and vecuronium are the only drugs of medium duration, and of these two vecuronium is the shortest acting. Neither drug causes ganglion blockade, sympathetic stimulation, vagolytic effects or vagal stimulation. Regarding histamine release, vecuronium is superior to

Table I Adverse effects and pharmacodynamic parameters of d-tubocurarine, pancuronium, vecuronium and atracurium

	d-tubocurarine	pancuronium	vecuronium	atracurium
ganglion blockade	++	-	-	-
sympathetic stimulation	-	++	-	-
vagolytic effect	-	++	-	-
vagal stimulation	-	-	-	-
histamine release	+++	-	-	+
onset time (sec)	221	215	168	161
recovery rate (min)	59	32	10	11
approximate relative potency by weight	1	4.7	5.6	1.1

atracurium. Considering all these factors, which are summarized in Table I, vecuronium is the drug of choise in the present investigations with paediatric patients.

IV THE POTENCY OF VECURONIUM IN NEONATES, INFANTS AND CHILDREN

Vecuronium is a nondepolarizing neuromuscular blocking agent with (in adults) an intermediate duration of action and a potency slightly greater than that of pancuronium. Potency can be expressed as the effective dose causing 50, 90 or 95% depression of an evoked muscle response (ED_{50}, ED_{90}, ED_{95}) and as a dose-response curve. The ED_{50}, ED_{90} and ED_{95} of vecuronium in adults have been calculated by various investigators.

In adults the effective doses were often calculated from a cumulative dose-response curve. In longer-acting relaxants this causes only minor deviations from the real value, but for vecuronium and atracurium it may cause larger deviations. Part of the previous dosage is already inactive by the time the next dose is given. Thus a cumulative technique then overestimates the effective dosages and causes a shift of the dose-response curve to the right.
The published ED_{50} values of vecuronium in adults vary from 12.8 to 31 mcg/kg, the ED_{90} from 36.5 to 45 mcg/kg and the ED_{95} from 39.6 to 56.7 mcg/kg, calculated using different techniques and procedures.

In infants only Fisher and Miller (1983) have calculated an ED_{50}: 16.5 mcg/kg. The ED_{90} or ED_{95} for this age group cannot be found in the literature. In children Meistelman and coworkers calculated the ED_{50}, ED_{90} and ED_{95} non-cumulative: respectively 31, 55 and 64 mcg/kg (Meistelman et al., 1986b). Goudsouzian and coworkers (1983a) used a cumulative technique and found respectively 33, 51 and 60 mcg/kg. Fisher gives the ED_{50} in children as 19.0 mcg/kg. For adolescents Goudsouzian and coworkers (1983a) calculated the cumulative ED_{50}, ED_{90} and ED_{95} to be, respectively, 23, 39 and 45 mcg/kg. All paediatric studies were conducted under halothane anaesthesia (Table II). Thus one concludes that data are scattered and rare, especially in the infant-group. The aim of the study presented here is to determine

Table II Pharmacodynamic data of VECURONIUM in various age groups

Investigator	Age	Anaesthesia	Monitoring technique	ED_{50} (mcg/kg)	ED_{90} (mcg/kg)	ED_{95} (mcg/kg)
INFANTS						
Fisher and Miller (1983)	7-45 weeks	0.9 MAC Halothane	M.M.G.-T_1	16.5	-	-
CHILDREN						
Fisher and Miller (1983)	1-8 yr	0.9 MAC Halothane	M.M.G.-T_1	19.0	-	-
Goudsouzian et al. (1983a)	2-9 yr	1.5% Halothane	M.M.G.-TOF	33[c]	51[c]	60[c]
Meistelman et al. (1986b)	4-8 yr	1% Halothane	E.M.G.-T_1	31	55	64
ADOLESCENTS						
Goudsouzian et al. (1983a)	10-17 yr	1.5% Halothane	M.M.G.-TOF	23[c]	39[c]	45[c]
ADULTS						
Gibson et al. (1985)	adult	Fentanyl	M.M.G.-T_1	23.1	-	39.6
Ording et al. (1985)	18-70 yr	Halothane	M.M.G.-T_1	25.7	36.5	-
	18-70 yr	Fentanyl	M.M.G.-T_1	28	40	-

[c] cumulative dose response

dose-response curves and to calculate the $ED_{50,90}$ and $_{95}$ in various age groups, using a uniform experimental procedure.

MATERIALS AND METHODS

The study was approved by the Hospital Ethical Committee. 211 healthy children, varying in age from 2 days-15 years old, body weight from 2.5-61 kg, were studied. All patients were free from respiratory, cardiovascular, neurological and infectious diseases. No patient suffered from metabolic, hepatic or renal disturbances. The gestational age of all patients younger than 5 years of age was 38 weeks or more. Antibiotics and diazepam were strictly avoided.

Each patient received an anaesthetic technique that was, so far as possible, standardized for these patients of such differing age groups (described below). The children were divided into 5 groups according to age: Group I 0-6 weeks old (n = 31); Group II 6-12 weeks old (n = 41); Group III 12 weeks-1 year old (n = 45); Group IV 1-6 years old (n = 48) and Group V 6 years old and over (n = 46) (Table III).

In group I 13 patients were operated for an inguinal hernia and 6 for pyloric stenosis. In group II the most frequent operations were herniotomy (n=34) and pyloromyotomy (n=4); and in group III herniotomy (n=22) and correction of cleft lip (n=7). In group IV 15 patients

Table III Number, age, weight and sex distribution. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-15 years

	n	Age	Weight	Male	Female
Group I	31	27.0 ± 12.6 days	3684 ± 603 g	24	7
Group II	41	60.1 ± 11.4 days	4753 ± 769 g	31	10
Group III	45	199 ± 93 days	7366 ± 1819 g	31	14
Group IV	48	2.9 ± 1.5 years	14.6 ± 3.7 kg	41	7
Group V	46	9.6 ± 2.2 years	34.2 ± 10.0 kg	31	15

Values (age and weight) are mean ± S.D.

underwent a herniotomy and 18 orchidopexia. In group V most patients were operated for undescended testes (n=20), 5 were operated on the middle ear and 4 underwent herniotomy.

Premedication was not given to infants with a body weight less than 3 kg. Infants with a body weight between 3 and 8 kg received 0.1 mg/kg atropine intramuscularly. Above 8 kg body weight 3 mg/kg trimeprazine (to a maximum of 60 mg) and 0.03-0.04 mg/kg atropine (to a maximum of 1 mg) were given orally, 2 hours before the estimated time of induction.

General anaesthesia was induced with 5 mg/kg thiopentone i.v. and fentanyl, 3 mcg/kg for children of 12 weeks and older (groups III, IV and V), and 1-3 mcg/kg for infants younger than 12 weeks of age (groups I and II). Anaesthesia was maintained with 67% nitrous oxide in oxygen. Volatile halogenated agents were never used. Immediately after induction ventilation was assisted or controlled, using a mask. The aim was to keep the patient normocapnic (4.5-5% end expiratory CO_2).

Immediately after induction surface electrodes for EMG recording were secured to the arm and 5 baseline electromyogram measurements were made (described later). Hereafter only once a single dose of vecuronium bromide was given intravenously. The intravenous canula was never in the same arm as the EMG-recording electrodes.
Intubation was not attempted when the patient received a low dose of vecuronium. In this case all measurements were made first and intubation followed later after a second dose of vecuronium. The body temperature was kept normal and constant using such devices as a heating shield and a warm-water blanket. The ECG was continuously monitored in every patient. Surgery was started when all EMG measurements, taking approximately 10 min, were finished.

The stimulus electrodes used in this study were small commercially available EEG electrodes (fig. 9). They were firmly taped to the skin of the elbow to stimulate the ulnar nerve. A wet ground electrode was wound around the forearm (fig. 10). The recording electrodes were taped to the hypothenar eminence and the base of the fifth finger. These electrodes were homemade and consisted of a small circular link (diameter 3.5 mm) from a silver necklace soldered to a lead (fig. 11).

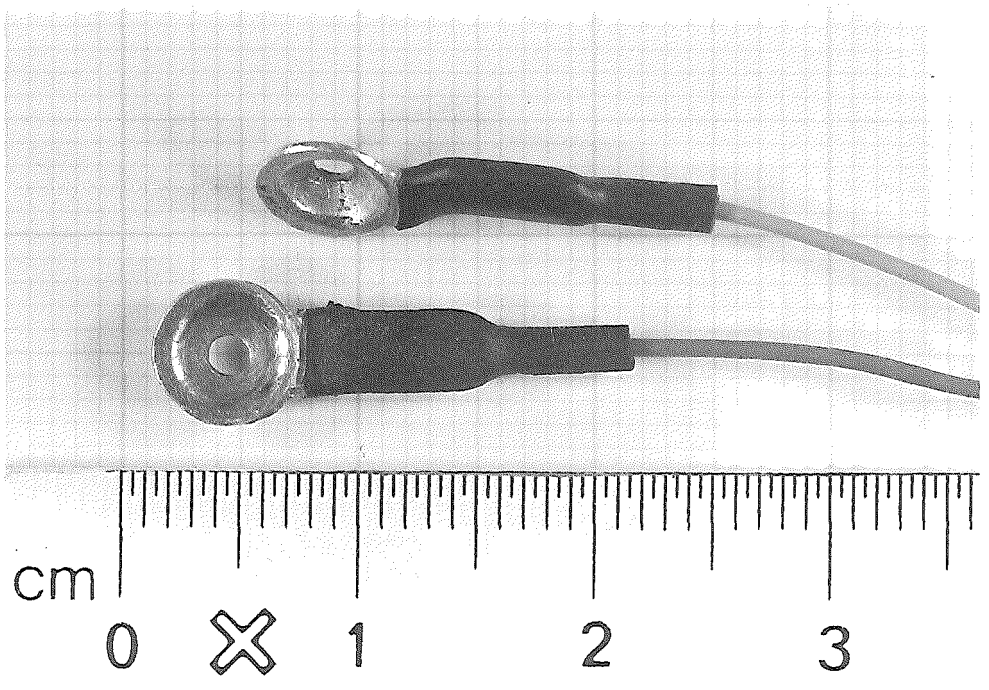
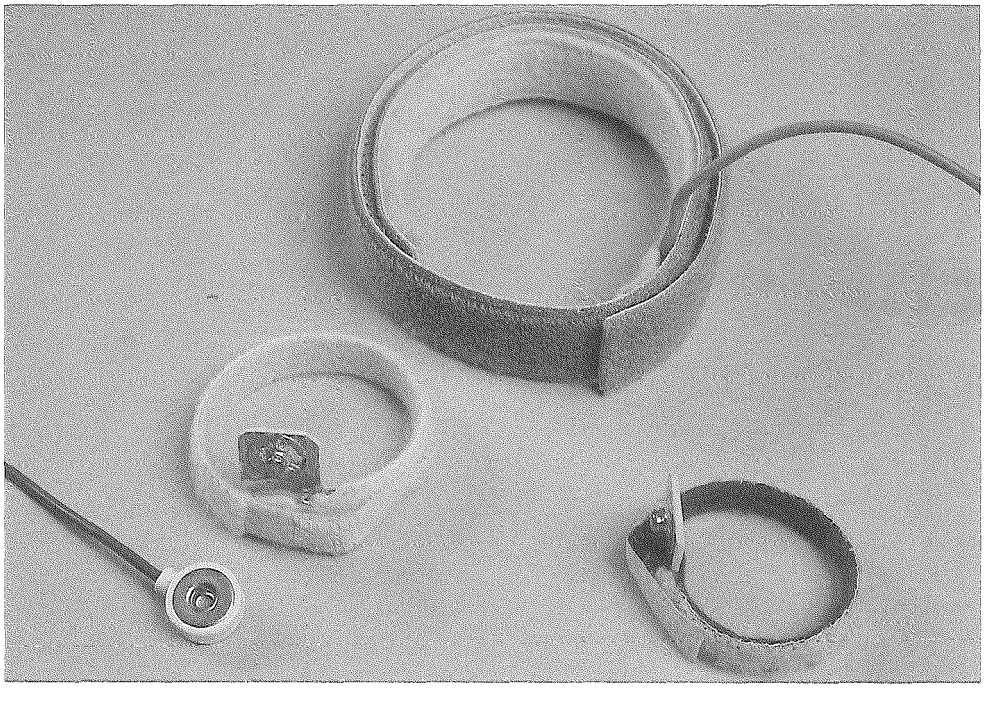


Fig. 9 Stimulus electrodes

Fig. 10 Ground electrodes



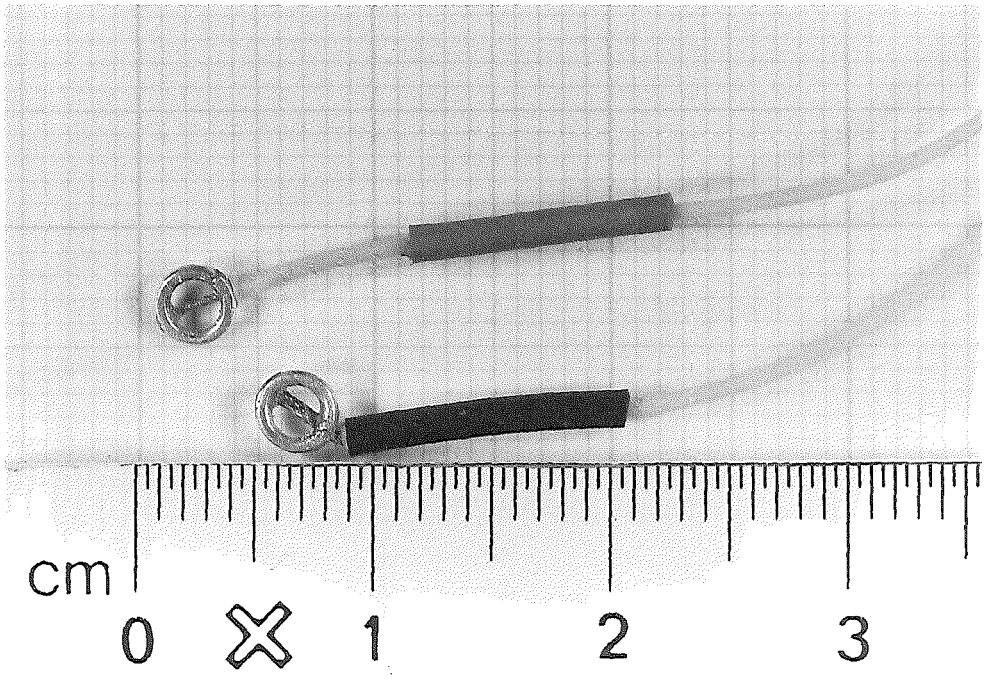
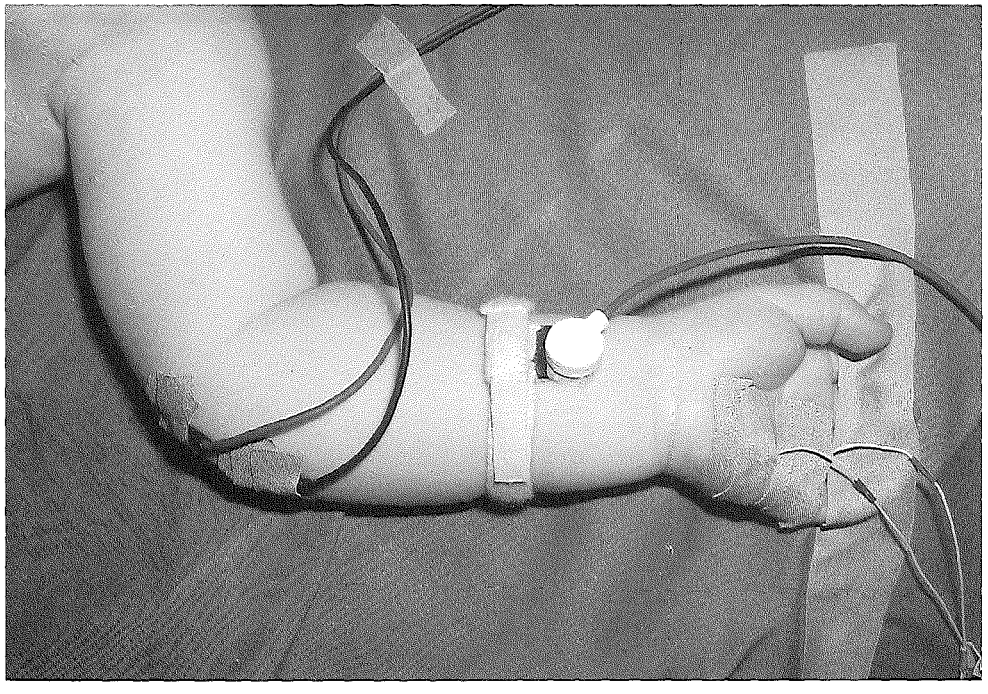


Fig. 11 Recording electrodes

Fig. 12 Arm with electrodes



Conductivity of stimulating and recording electrodes was improved by using EEG-gel. Care was taken to avoid contact of gel between one electrode and the other. The fingers were taped to the table to avoid gross movements of the hand (fig. 12).

The electromyographic responses were measured with a Medelec MS 91, a diagnostic electromyograph (fig. 13). With this machine the stimulus is adjustable in many ways. After stimulation of the ulnar nerve the resultant electromyogram was displayed on the oscilloscope of the Medelec monitor. From the memory, every response can be written on paper by a slow recorder in the Medelec. Thereby artefacts can be sorted out easily (fig. 14).

The ulnar nerve was stimulated by a single supramaximal, squarewave stimulus of 0.1 Hz with a duration of 0.2 msec.

The negative deflection of the single EMG-response taken from the Medelec paper was used to estimate muscle relaxation. The mean of the first 5 control measurements served as control (0% relaxation). No measurable deflection was considered to correspond with 100% blockade of neuromuscular transmission. Every 10 seconds the degree of blockade (% of response compared to control value) was measured until it reached its maximum and was stable, or until recovery began. The maximum block was used for data analysis.

Within each group all different dosages were used and applied in strict random order. Within each age group responses as % of maximal blockades into probits (Finney, 1952) were related to dosages transformed to natural logarithm (ln).

Within each of the 5 groups the patients, receiving the same dosage vecuronium per kg bodyweight, were considered a sub-group (Table IV). The percentage response from all individuals in a sub-group were taken and their mean and standard deviation calculated. From the sub-groups results a dose-response curve was formed per age group.

A common way of expression is to use a logarithmic scale for the dose-axis and a linear scale for the response-axis. The resultant curve will then be S-shaped. To simplify matters, the curve is transformed to a straight line when for the dose a log scale (^{e}log) and for the response a probit scale is used. Thus a log-probit dose-response curve was estimated for all 5 groups. The log-probit

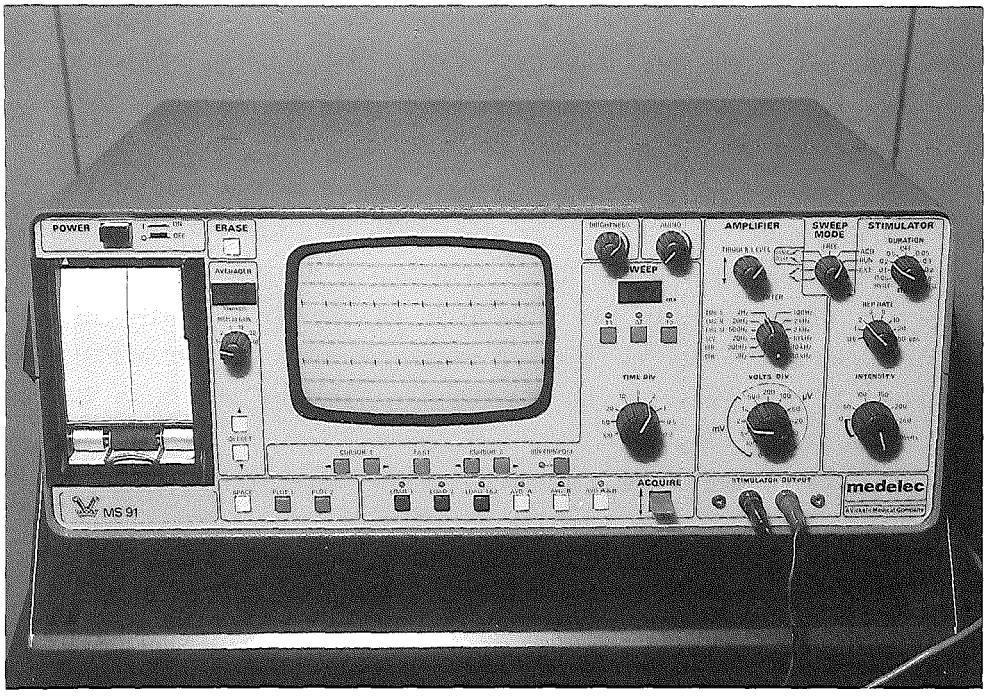


Fig. 13 Medelec MS 91, diagnostic electromyograph

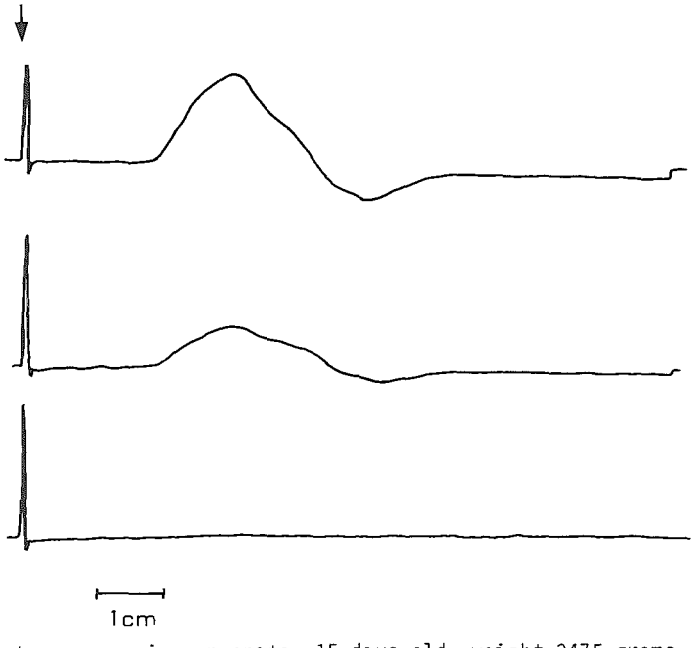


Fig. 14 Electromyogram in a neonate, 15 days old, weight 3475 grams. Control, 50 sec and 5 min after administration of 0.1 $mg.kg^{-1}$ vecuronium. Arrow indicates stimulus

Table IV Subgroups dose-response curves

		Number of individuals receiving dose ($mg.kg^{-1}$) vecuronium										
Group	n=	0.01	0.015	0.02	0.25	0.03	0.04	0.05	0.06	0.08	0.1	0.12
I	31	1	5	5	0	5	0	5	5	5	0	0
II	41	5	5	5	5	5	0	5	5	6	0	0
III	45	5	5	5	5	5	5	5	5	5	0	0
IV	48	0	5	6	5	6	0	5	5	5	6	5
V	46	0	5	6	5	5	0	5	5	5	5	5

dose-response curves are described by the formula $y = a + bx$.
Linear equations were computed using the model $y = a + bx$, with y as the probit of the response; a as the intercept of the line with the y-axis; b as the slope of the line and x as the natural logarithm of the dose. The estimated value of x at a particular response level follows from $x = \frac{y-a}{b}$.

Thus the ED_{50}, the effective dose which results in 50% block, is obtained at the probit of 50%, which is $y = 5.0$; therefore

$$x = \ln ED_{50} = \frac{5.0-a}{b}.$$

The intercepts a and the slopes b were estimated from the data using a computer program (Quickstat 64, Scattergram). In a similar way the ED_{90} and ED_{95} were calculated for each age group. To compare the results between the 5 age groups the 95% confidence limits for $\ln ED_{50}$, $\ln ED_{90}$ and $\ln ED_{95}$ were calculated using the formula $\ln EDp \pm t * SE(\ln EDp)$, where t is read from a Student-t table. The

SE (ln EDp), the standard error of the ln EDp was calculated using the formula:

$$SE\ (\ln EDp) = \sqrt{\frac{(T_p - \bar{y})^2 * [SE(b)]^2 + b^2 * [SE(\bar{y})]^2}{b^4}}$$

where T_p is the probit corresponding to the relevant percentage P (50, 90, 95) and $\bar{y}$ is the mean of the y-values in the group concerned.

$[SE(b)]^2 = \frac{\text{residual variance}}{\sum(x-\bar{x})^2}$, where $\bar{x}$ is the mean of the x-values in the group and

$$\text{residual variance} = \frac{\sum(y - \bar{y})^2 - b^2 \sum(x - \bar{x})^2}{n - 2}$$

$$[SE(\bar{y})]^2 = \frac{\text{residual variance}}{n}$$

RESULTS

Data obtained from all patients were used for analysis, except for a few patients (not enlisted in Table IV), who were excluded due to technical failures. The resultant dose-response curves are shown in fig. 15.

Using the above described formula, the log-probit dose-response curves were computed for the various groups:

Group I $y = 12.49 + 2.08x$ n=31
Group II $y = 12.18 + 1.98x$ n=41
Group III $y = 12.57 + 2.13x$ n=45
Group IV $y = 11.17 + 1.98x$ n=48
Group V $y = 11.28 + 2.00x$ n=46

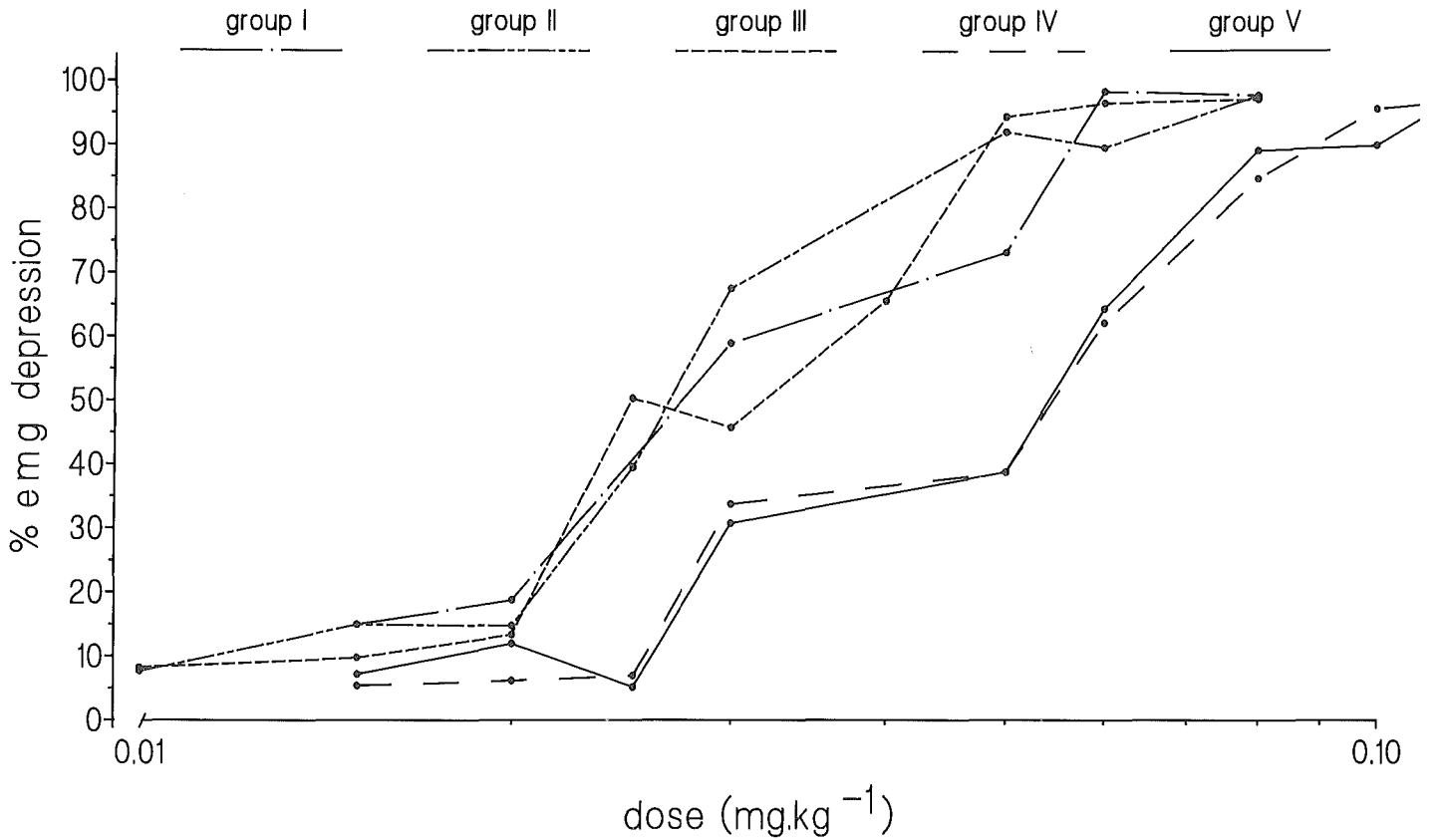


Fig. 15 Dose-response (mg.kg^{-1} - % EMG depression) curves for vecuronium. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-15 years

The log-probit dose-response curves are given in figure 16.
From the log-probit curves obtained for each of the 5 groups, the ED_{50} (effective dose for 50% block), ED_{90} and ED_{95} plus the 95% confidence limits (in brackets) (fig. 17) were calculated using equations above.

The ED_{50} in group I is 0.027 mg/kg (0.024-0.031).
The ED_{50} in group II is 0.027 mg/kg (0.024-0.029).
The ED_{50} in group III is 0.028 mg/kg (0.025-0.032).
The ED_{50} in group IV is 0.044 mg/kg (0.040-0.048).
The ED_{50} in group V is 0.044 mg/kg (0.040-0.048).

The ED_{90} in group I is 0.050 mg/kg (0.043-0.059).
The ED_{90} in group II is 0.051 mg/kg (0.045-0.058).
The ED_{90} in group III is 0.052 mg/kg (0.044-0.056).
The ED_{90} in group IV is 0.084 mg/kg (0.074-0.096).
The ED_{90} in group V is 0.083 mg/kg (0.072-0.095).

The ED_{95} in group I is 0.060 mg/kg (0.050-0.072).
The ED_{95} in group II is 0.061 mg/kg (0.053-0.070).
The ED_{95} in group III is 0.062 mg/kg (0.051-0.074).
The ED_{95} in group IV is 0.101 mg/kg (0.087-0.117).
The ED_{95} in group V is 0.099 mg/kg (0.085-0.116).

A significant difference ($p < 0.05$) was found in effective doses between infants up to 1 year of age (groups I, II and III) and children of 1-15 years of age (groups IV and V). Very similar results were found for neonates of 2 days-6 weeks of age (group I), infants of 6-12 weeks of age (group II), 12 weeks-1 year of age (group III) on the one hand and for children of 1-6 years of age (group IV) and children and adolescents of 6-15 years of age (group V) on the other hand. Figure 15 and 17 clearly show these results. The ED_{50}, ED_{90} and ED_{95} each show a similarity between group I, II and III on the one hand and group IV and V on the other.

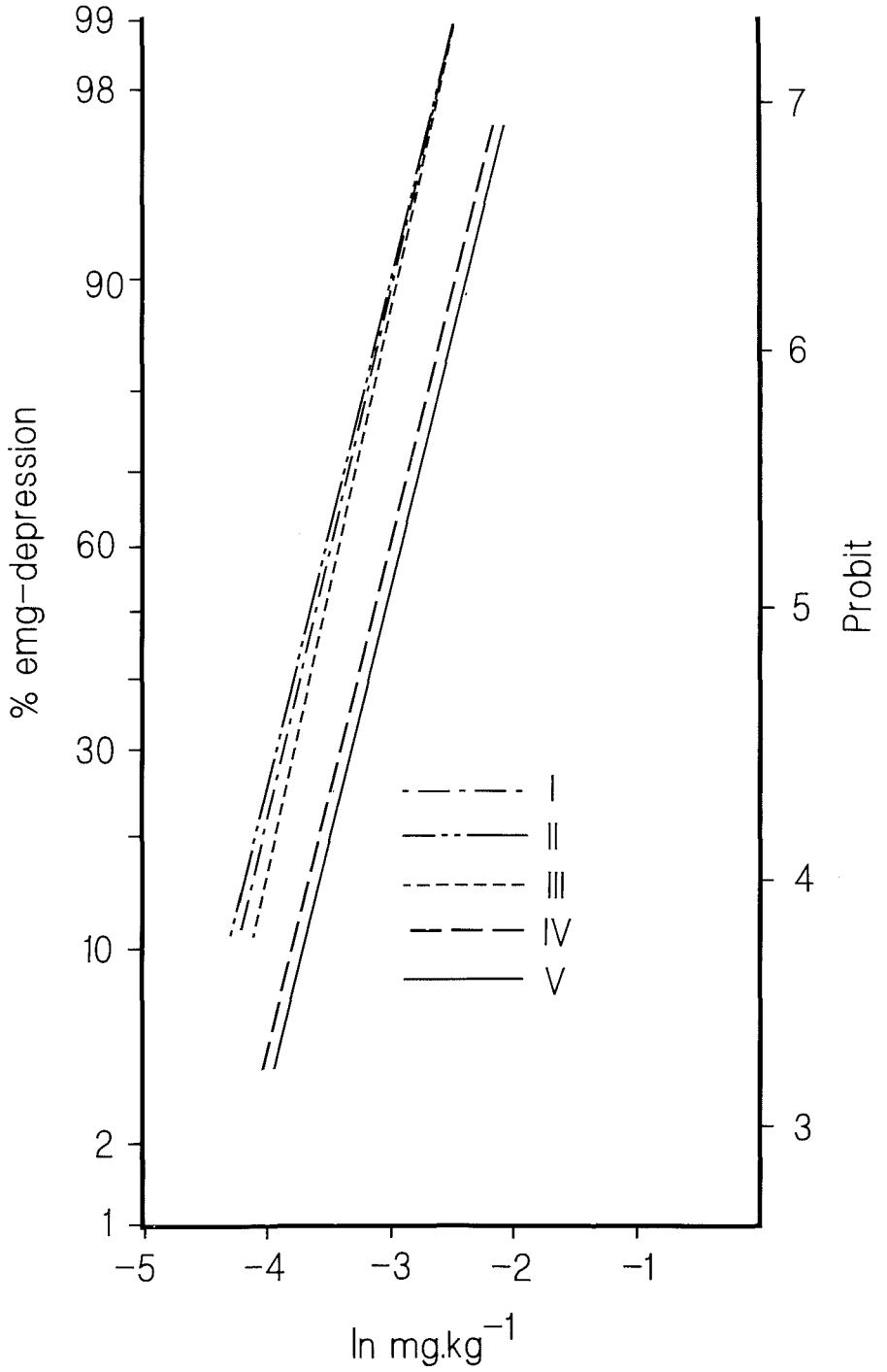


Fig. 16 Dose-response (ln mg.kg^{-1} - probit % EMG depression) curves for vecuronium. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-15 years.

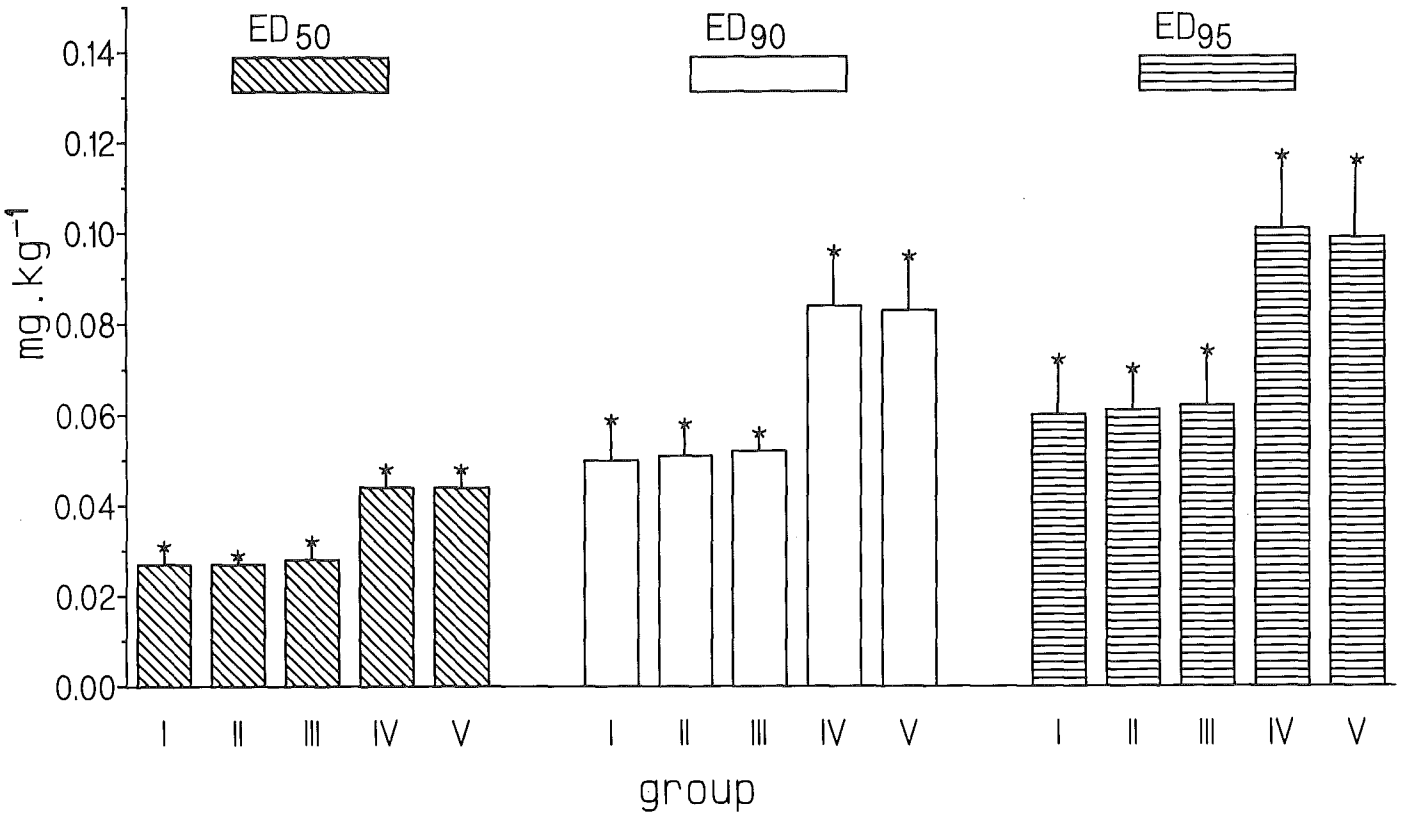


Fig. 17 Effective doses ($mg.kg^{-1}$) causing 50, 90 and 95% EMG depression ($ED_{50,90,95}$) of vecuronium ± 95% confidence limits. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-15 years

DISCUSSION OF THE METHODOLOGY

Halogenated anaesthetic agents potentiate neuromuscular blockade induced by nondepolarizing muscle relaxants in a dose-dependent manner (see Chapter II). Fisher criticizes other authors for using a fixed concentration of halothane in different age groups. He states that anaesthetic conditions comparable for neonates, infants, children and adults are created by using equivalent, age adjusted MAC fractions of halothane (Fisher, Miller, 1983). However the MAC of halogenated agents is simply a mean value. Considerable interindividual differences may exist. The effect of halogenated agents on neuromuscular transmission is dose-dependant. But it is unknown as to whether using equivalent MAC fractions of halothane in patients of various ages provides equal effect on the pharmacodynamics and pharmacokinetics of vecuronium bromide. We therefore performed our study without the use of volatile anaesthetics.

As with the anaesthetic technique, the stimulating and measuring techniques should also be standard in each group. Chosen is for a single twitch stimulation, because with this technique mainly postsynaptic effects are measured, whereas in train-of-four stimulation the presynaptic effect is more involved. In neonates the train-of-four ratio value without relaxants can be less than 100%, thus in this way even baseline measurements will be unequal. Stimulus duration is chosen to be 0.2 msec. Supramaximal stimulation is thereby obtained easier than with a stimulus of shorter duration. The abundant subcutaneous fat in infants can be especially troublesome in this respect. Longer stimulation is not advisable due to the possibility of repetitive firing.

For quantitation of effect the electromyogram was chosen, being a more direct method than force of thumb adduction and for practical reasons being easier applied to infants and children. The amplitude of the negative deflection of the EMG-response was used to calculate the response. This is an easy method and has no disadvantages over calculating negative and positive amplitude or integration of the area under the curve (Pugh et al., 1984).

The ulnar nerve is stimulated in order to be consistent with other

investigations, thus making comparison easier. The hypothenar muscles are measured because this location is less subject to movement artifact caused by twitch-related movement of the hand. Moreover the hypothenar muscles are more superficial than the thenar muscles, thus the amount of tissue between muscles and recording electrodes is minimized, reducing the likelihood of measurement artifacts (Weber, Muravchick, 1986). Strict randomization of order of applying doses within age groups was followed to eliminate artefacts and bias in estimation of responses.

DISCUSSION

Confusion still remains concerning the sensitivity of children to nondepolarizing neuromuscular blocking agents. In the attempt to compare different age groups, it is essential to first clearly define what is meant by sensitivity. Does this refer to the correlation between dose and response, to the duration of the (clinical) effect or to both? In this study a comparison was made between five different age groups, ranging from neonates to adolescents, investigating the correlation between dose and response. We found a significant difference between children under 1 year of age and those over 1 year of age.

The physiologic changes associated with maturation constitute a complex situation, with drugs localizing in different body regions, depending upon age. Although apparent volumes of distribution measured pharmacokinetically do not correspond to true body compartments, one would expect that age-related changes in body composition would be reflected in the measured distribution volumes. Most drugs distribute throughout the extracellular water before reaching their receptor sites. Particularly for drugs that are minimally distributed in the tissues (Boreus, 1982), such as muscle relaxants (Roland, 1978), the size of the extracellular water influences the drug concentration. The extracellular water decreases with age, especially in the first year of life (Widdowson, 1981). Thus as a rule, to achieve a given plasma concentration for drugs distributed in the extracellular water, a higher dose for each kilogram of body weight must be administered in

the neonate and infant compared to the adult (Martyn, 1986). These age-related variations in pharmacokinetics are further compounded by differences in receptor sensitivity between the various age groups. Whereas, on the basis of extracellular water, one would expect the neonate to be less sensitive to relaxant drugs given per kg body weight, on the basis of maturation of the neuromuscular system one would expect them to be more sensitive. Goudsouzian (1980) found that maturation of neuromuscular transmission occurs in the first two months after birth. Crumrine and Yodlowski (1981) demonstrated a difference in myoneural function between that of infants less than 12 weeks of age and that of older children and adults. It is thus not surprising that in our study infants up to 12 weeks of age (group I and II) are more sensitive to vecuronium. The balance between immaturity of the neuromuscular system and the increased extracellular water favors the former. Yet it is surprizing that the same results are found for infants from 12 weeks-1 year of age and that such a clear division is found between this age group and children of 1 year and older. Other mechanisms involving the neuromuscular transmission and/or organ function must therefore exist.

Comparing results of different investigators it is essential to realise that the human adductor pollicis muscle contains approximately 80% slow fibres and the abductor digiti minimi 52% (Johnson et al, 1973). Thus a difference may be found between studies using thenar muscles and those using hypothenar muscles. Yet Katz (1973) found a good correlation of EMG-% block in thenar and hypothenar muscles after suxamethonium administration. Our measurements were made on the hypothenar eminence. All undermentioned studies were performed measuring EMG or MMG of the adductor pollicis muscle.

Fisher and Miller (1983) found infants (7-45 weeks old, ED_{50} 16.5 mcg/kg) to be more sensitive than children (1-8 years old, ED_{50} 19.0 mcg/kg) and adults to be more sensitive than infants and children (ED_{50} 15 mcg/kg). But as a statistically significant difference did not exist, they concluded that vecuronium can be used in infants and children in doses similar to those recommended for adults during anaesthesia with nitrous oxide and 0.9 MAC halothane.

Goudsouzian and coworkers (1983a) found children (2-9 years old,

ED_{50} 33 mcg/kg) significantly more resistant to the neuromuscular effects of vecuronium than adolescents (10-17 years old, ED_{50} 23 mcg/kg) during anaesthesia with 1-1.5% halothane, using a cumulative technique. Meistelman and colleagues (1986b) only measured one group of children (4-8 years old) and found the ED_{50} to be 31 mcg/kg during 1% halothane anaesthesia. No comparison can be made because of the differences between the protocols. Different amounts of halothane were used, cumulative and noncumulative dose-response curve techniques and monitoring with either EMG or MMG were applied. The EMG response is likely to be less decreased than the MMG during halothane anaesthesia (Epstein and Epstein, 1973). However the ED_{50}'s found by Fisher with comparable techniques are comparatively low.
In our study no halogenated agents were used. Thus the expected effective doses should be higher than those found in studies using halothane. The calculated effective doses came up to this expectation.

There are no comparable studies in adults. Gibson and coworkers (1985) and Örding and colleagues (1985) both used fentanyl anaesthesia and MMG, single twitch compared to control. They found ED_{50}'s respectively 23.1 and 28 mcg/kg. Gibson and colleagues found the ED_{95} to be 39.6 mcg/kg and Örding and coworkers the ED_{90} to be 40 mcg/kg. Their ED_{50}'s correlate well with the ones calculated in our study for neonates and infants. The ED_{90} and ED_{95} for the same groups are however much higher compared to the results of Gibson and Örding. An explanation for this may be the slight difference in the slope of the dose-response curve causing a major difference in the far-ends of the curve. Thus a small difference in the slope of a curve with the same ED_{50} causes a major difference in the calculated ED_{95}. The effective doses calculated for groups IV and V are much higher than the ones published by Gibson and Örding for adults. Thus it is suggestive that the potency of vecuronium is higher in adults than in children and adolescents. In conclusion our study shows the potency of vecuronium in children up to 1 year of age to be higher than in children of 1-15 years of age when given on the basis of body weight.

V ONSET TIME, DURATION OF ACTION AND RECOVERY RATE OF VECURONIUM IN NEONATES, INFANTS AND CHILDREN

Vecuronium and atracurium are nondepolarizing neuromuscular blocking agents, developed in the search for the ideal muscle relaxant. Some of the requirements for such an ideal muscle relaxant are a fast onset, a short duration of action and a fast recovery. Although succinylcholine exerts such a pharmacodynamic profile it is a depolarizing drug and due to its many adverse effects, is not favoured in paediatric anesthesia. d-Tubocurarine and pancuronium, currently the most frequently used nondepolarizing muscle relaxants are characterized by a slow onset, a long duration of action and a slow recovery.

Fisher and Miller (1983) and Motsch et al. (1985) have published data on the onset time (time from injection to maximal blockade) and recovery time of a vecuronium-induced neuromuscular blockade in infants. Both found a rapid onset after 70 mcg/kg of respectively 1.5 and 1.4 min. In children they found onset times of respectively 2.4 and 2.7 min. More data on onset times regarding children, adolescents and adults have been published by various authors (Table V). The onset time appeared to be dependant on the administered dose: a small dose causing a longer onset time, whereas a larger dose resulted in a shorter onset time. But beyond a certain dose the onset time does not further decrease (Bencini, Newton, 1984).

The clinical duration (the time from injection to a recovery of 75% blockade) after a dose of 70 mcg/kg vecuronium, under halothane anaesthesia, was found to be 25 min in infants, 18 min in children (Motsch et al., 1985) and 22 min in adults (Engbaek et al., 1984).

Recovery of neuromuscular blockade is generally expressed as the time from injection or maximal effect to a certain percentage of recovery, or as the recovery rate (the time from 75-25% blockade). Here too the anaesthesia and monitoring technique play an important role. These factors and the given dose of relaxant vary considerably

Table V Pharmacodynamic data of VECURONIUM in various age groups

Investigator	Age	Anaesthesia	Monitoring technique	Dose of vecuronium (mcg/kg)	Onset (min)	Recovery time (min) 5%	25%	90%	95% of control	Recovery rate (min) 25-75%
INFANTS										
Fisher and Miller (1983)	7-45 weeks	0.9 MAC Halothane	M.M.G.-T_1	70	1.5	-	-	73	-	20
Motsch et al. (1985)	1 day-10 months	Halothane	E.M.G.	70	1.4	-	25	-	-	18
CHILDREN										
Fisher and Miller (1983)	1-8 yr	0.9 MAC Halothane	M.M.G.-T_1	70	2.4	-	-	35	-	9
Goudsouzian et al. (1983a)	1-10 yr	1-1.5% Halothane	M.M.G.-T_1	120	2.2	21.4	27.2	-	44.6	10.5
Meistelman et al. (1986b)	4-8 yr	1% Halothane	E.M.G.-T_1	100	3.1	-	-	36.5	-	9.3
Motsch et al. (1985)	1-6 yr	Halothane	E.M.G.	70	2.7	-	18	-	-	10
ADOLESCENTS										
Goudsouzian et al. (1983a)	11-17 yr	1.5% Halothane	M.M.G.-T_1	80	1.8	19.7	26.5	-	48.1	13.1
ADULTS										
Bencini, Newton (1984)	20-70 yr	Thiopentone	M.M.G.-T_1	100	3.4	-	21.0*	-	-	10
Engbaek et al. (1984)	adult	Ketamine	M.M.G.-TOF	73	2.5	-	22.2	-	-	-
Foldes et al. (1983)	adult	Fentanyl	M.M.G.-T_1	100	5.4	-	38.3*	-	-	-
Robertson et al.(1983a)	18-65 yr	Fentanyl	M.M.G.-T_1	129	2.6	-	39.0*	52.6*	-	13.8

* from injection

between different studies and make comparison of various studies almost impossible. The recovery rate seems to be the best method for comparing different age groups, because it is determined mainly by the disappearance of the muscle relaxant from the receptor side. Because vecuronium-induced neuromuscular blockade does not show a cumulative effect (Agoston et al., 1980) the recovery rate is less dependant on the given dose of vecuronium as are recovery times taken from injection or maximal effect, which are also determined by other factors.

All published paediatric studies were carried out under halothane anaesthesia. Onset time may be influenced by halogenated agents, because these agents potentiate the intensity of vecuronium-induced neuromuscular blockade (Rupp et al., 1984) and because these agents have cardiovascular effects, changing muscle perfusion and other parameters. A decrease in hepatic blood flow (Gelman, 1976) can alter the distribution and elimination of the relaxant by the liver (Meistelman et al., 1986b; Martyn, 1986). Thus halogenated agents also influence recovery. Cardiovascular effects of halogenated agents are more pronounced in neonates and infants than in children and adults. Thus one cannot presume that an equal inhalational concentration of halothane, even if this concentration is adjusted to the MAC for the age of the patient, has an equal effect on onset and recovery in the various age groups. Therefore this study, comparing onset and recovery of vecuronium-induced neuromuscular blockade in different paediatric age groups, is performed without the use of volatile anaesthetic agents.

MATERIALS AND METHODS

The study was approved by the Hospital Ethical Committee. Latency times and onset times were measured in the 211 patients described in Chapter IV, given various single dosages and measured every 10 seconds. The recovery phase was studied in 52 healthy children, others than the 211 described in Chapter IV, varying in age from 0 days to 13 years of age and in weight from 2460 g -54 kg. All patients were free from respiratory, cardiovascular, neurological and infectious

diseases. No patient suffered from metabolic, hepatic or renal disturbances. The gestational age of all patients younger than 5 years of age was 38 weeks or more. Excluded from studies during the recovery phase were patients needing good surgical relaxation and patients scheduled for operations with an expected blood loss of more than 5% of the circulating blood volume. Antibiotics and diazepam were strictly avoided.

The 52 children were divided into the same 5 age groups as described in Chapter IV.

In group I 6 patients were operated for pyloric stenosis, 4 underwent a small laparotomy and 1 patient was operated for inguinal hernia. In group II 9 patients were operated for inguinal hernia and two for pyloric stenosis. In group III 7 patients underwent herniotomy, 1 patient pyloromyotomy and 2 patients diagnostic procedure. In group IV and V 6 respectively 7 patients underwent orchidopexia and the others minor procedures. Number, mean age and weight and sex distribution of the patients of the different groups are shown in Table VI.

Each patient received a standardized anaesthetic technique as far as is possible in patients of such varying ages. Premedication and induction were as described in Chapter IV. Anaesthesia was maintained with 67% nitrous oxide in oxygen, supplemented with small doses of fentanyl (1 mcg/kg) or thiopentone (1-2.5 mg/kg) if necessary. Volatile anaesthetic agents were strictly avoided.

Table VI Number, age, weight and sex distribution. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-13 years

	n	Age	Weight	Male	Female
Group I	11	21.7 ± 14.9 days	3336 ± 729 g	7	4
Group II	11	61.5 ± 12.0 days	4314 ± 465 g	9	2
Group III	10	157 ± 85 days	6140 ± 1003 g	5	5
Group IV	10	3.7 ± 1.7 years	16.3 ± 4.7 kg	8	2
Group V	10	10.4 ± 1.7 years	37.9 ± 11.8 kg	9	1

Values (age and weight) are mean ± S.D.

Immediately after induction the EMG electrodes were secured to the arm and 5 baseline EMG measurements were made. Hereafter in all 52 patients a single dose of 0.1 mg/kg vecuronium was given rapidly intravenously. The intravenous canula was never in the same arm as the EMG electrodes. Intubation was performed after 2-3 min. The patients were artificially ventilated and the percentage expired CO_2 was kept close to 4% (Gould Godart capnograph mark III). The temperature was kept normal and constant using such devices as a heating shield, and a warm water blanket. All patients were monitored using ECG and plethysmograph. Blood pressure (Dynamap), inspiratory O_2 and body temperature were also measured.

The electromyographic responses were measured using the same method as described in Chapter IV. The stimulus frequency was however lower than 0.1 Hz. During the 5 five minutes of the recovery studies measurements were done every half minute, thereafter every five minutes. This ensures that, even in the neonate, exhaustion never occured. Measurements were ceased on completion of the operation or after one hour, whichever came first.

Measurements were made in patients of different age groups in random order. Patients fitting into the selection criteria were scheduled for operation,independant of their ages. All 52 patients were used for calculations of percentages of blockade for as long as measurements could be made during maximally 60 minutes after injection of vecuronium. The recovery of the blockade induced by 0.1 mg/kg vecuronium was expressed in various ways: graphically in time, as recovery rate and calculated as slope of the recovery curve, clinical duration and duration to 10 and 5% EMG depression. Within each group the percentages blockade at 5 min intervals were calculated for each individual. Because not all patients could be measured during 60 minutes, the number of individuals used to calculate means and standard deviation decreased with increasing time after injection.

As many patients in groups I, II and III did not reach 75% recovery (25% EMG depression) within the period measurements were taken, recovery was expressed as the slope of the recovery curve. For each individual the slope of the recovery was estimated from the data using a computer programme (Epistat). Once EMG depression was less than

maximal, the relation between time after the end of injection and the percentage EMG depression was expressed in a linear equation:
$y = a + bx$ (y is the percentage EMG depression; a is the intercept of the line with the y-axis; b is the slope of the recovery and x is the time after end of injection).

Within each group the means of the individual a and b were calculated. The corresponding 95% confidence limits of b were calculated using the formula:

$$\text{mean} \pm \text{Student } t * \text{SE (mean)}$$

(the degree of freedom is n-1).

Using the formula $x = \frac{y-\bar{a}}{\bar{b}}$ it is possible to calculate time from the end of injection to a recovery of a certain percentage of EMG depression ($\bar{a}$ is the mean of the individual a's and $\bar{b}$ is the mean of the individual b's). The recovery times of the various age groups were calculated for a recovery to 75% (clinical duration), 10% and 5% EMG depression. Similarly the recovery rate was calculated for each age group. In groups IV and V the recovery rate was also measured in a conventional way, calculating the mean and standard deviation of the individual results.

The latency times (end of injection to first effect) and the onset times (end of injection to maximal effect) were calculated as the mean of the individual times ± standard deviation per group and per dose. Comparisons were made using the 95% confidence limits. To prove a correlation between age and latency or onset time the Spearman rank correlation coefficient was calculated using the formula as described in Chapter VI.

RESULTS

Not all 52 measured patients were used for analysis of the slope of the recovery. Some neonates in groups I and II did not recover a measurable amount in the available time thus had to be excluded: 2

patients of group I and 1 patient of group II were not included. One patient of group V was excluded because enflurane had to be administered to the patient shortly after the start of the measurements. The measured recovery in the various age groups is shown in fig. 18.

The calculated formula $y = \bar{a} + \bar{b}x$ is for:

group I	y = 124.87 - 1.18 x	n= 9
group II	y = 132.17 - 1.72 x	n=10
group III	y = 134.29 - 1.74 x	n=10
group IV	y = 152.41 - 4.48 x	n=10
group V	y = 138.88 - 3.89 x	n= 9

The calculated slope of the recovery (b) with the 95% confidence limits is for groups I to V respectively: -1.18 ± 0.76, -1.72 ± 0.98, -1.74 ± 0.92, -4.48 ± 0.74 and -3.89 ± 0.55 (fig. 19). A statistically significant difference is seen between groups I, II and III on the one hand and groups IV and V on the other ($p < 0.05$). The recovery in children of one year of age and older is faster than the recovery in neonates and infants.

The calculated times from the end of injection to 75% EMG depression (25% of control) are in groups I to V respectively 42.4, 33.2, 34.2, 17.3 and 16.4 minutes. Measured from the available data, the time to 75% EMG depression is in group I 40.0 ± 9.9 min (n=6), in group II 36.4 ± 9.8 min (n=5), in group III 37.0 ± 15.7 min (n=7), in group IV 18.7 ± 3.6 min (n=10) and in group V 18.0 ± 4.7 min (n=9). The calculated times to 10% EMG depression (90% of control) are in groups I to V respectively 97.7, 70.9, 71.6, 31.8 and 33.1 min and to 5% EMG depression (95% of control) respectively 102.0, 74.0, 82.4, 32.9 and 34.4 min (fig. 20).

The recovery rates (75-25% EMG depression) are calculated in all five groups. One patient of group IV and one of group V did not recover to 25% EMG depression, so had to be excluded. In groups I to V the calculated recovery rates are respectively 42.5, 29.0, 28.8, 11.2 and 12.9 min (fig. 21). The "conventional" recovery rate in group IV is 9.9 ± 2.4 min and in group V 10.9 ± 2.6 min (Table VII).

The latency times with the 95% confidence limits for the ED_{50} of

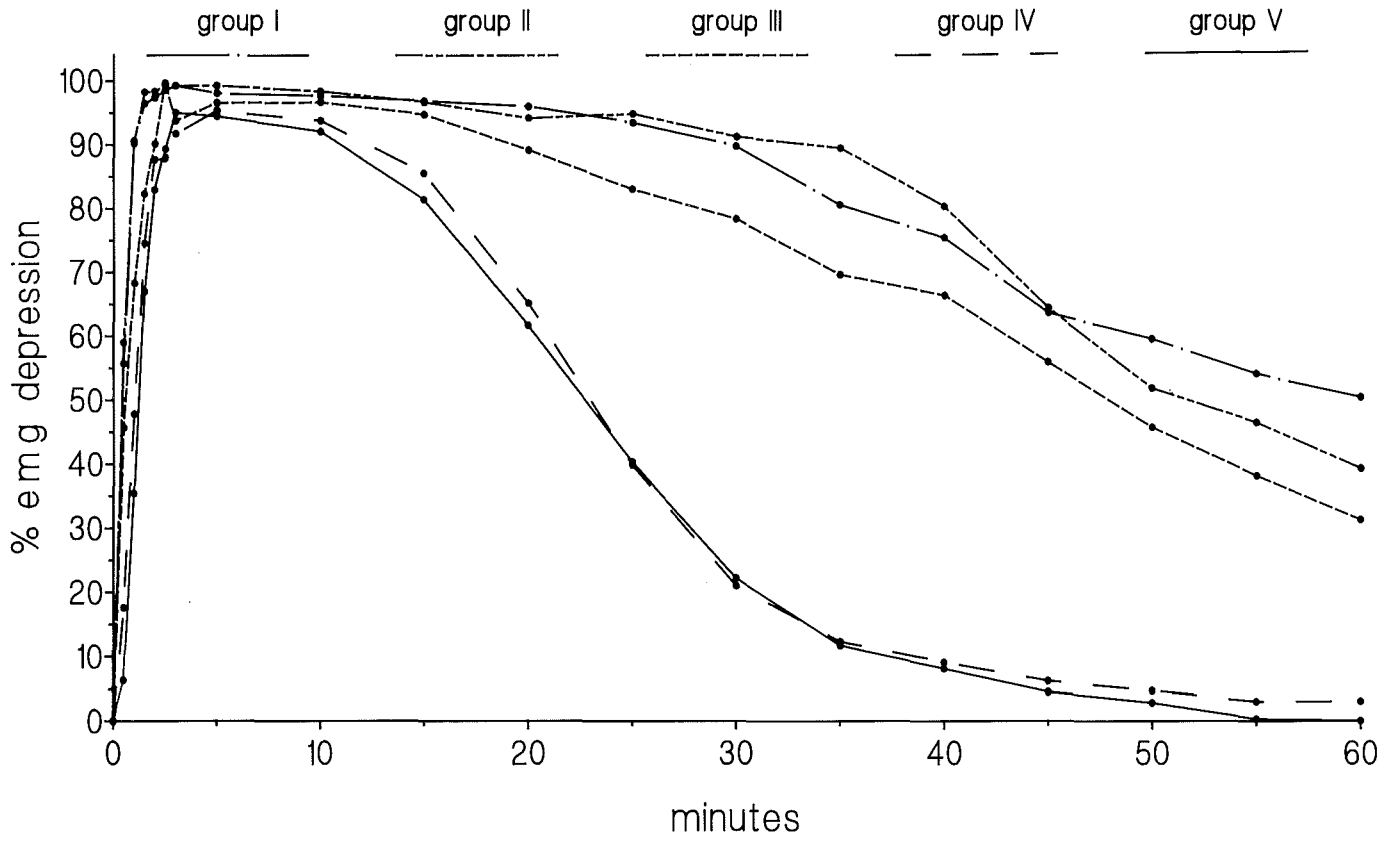


Fig. 18 Recovery (minutes) of the % EMG depression after administration of 0.1 mg.kg^{-1} vecuronium. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-13 years

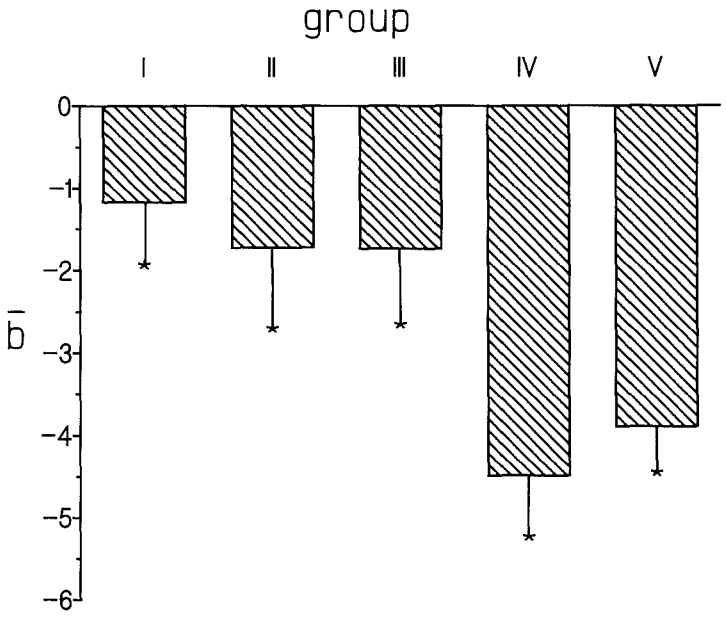


Fig. 19 Calculated slope of the recovery ($\bar{b}$) ± 95% confidence limits. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-13 years

vecuronium are in groups I to V respectively 20 ± 14 sec, 26 ± 18 sec, 15 ± 8 sec, 36 ± 15 sec and 42 ± 25 sec. No statistically significant differences were found, but the Spearman's rank correlation coefficient shows a positive correlation between age and latency time (alpha = 0.05). For the ED_{95} the latency times with the 95% confidence limits are in groups I to V respectively 13 ± 6 sec, 24 ± 6 sec, 20 ± 8 sec, 25 ± 12 sec and 38 ± 15 sec (fig. 22). There is a statistically significant difference between groups I and V. There is a positive correlation between age and latency time (alpha = 0.02, Spearman).

The onset times with the 95% confidence limits for the ED_{50} of vecuronium are in groups I to V respectively 188 ± 72, 232 ± 86, 250 ± 80, 264 ± 22 and 288 ± 33 sec. No statistically significant differences were found between the various age groups. But the Spearman's rank correlation coefficient shows a positive correlation between age and onset time (alpha = 0.01). The ED_{95} doses show onset times with 95% confidence limits in groups I to V of 180 ± 95 sec, 218 ± 70 sec, 188 ± 69 sec, 252 ± 60 sec and 210 ± 64 sec (fig. 23). Neither a statisti-

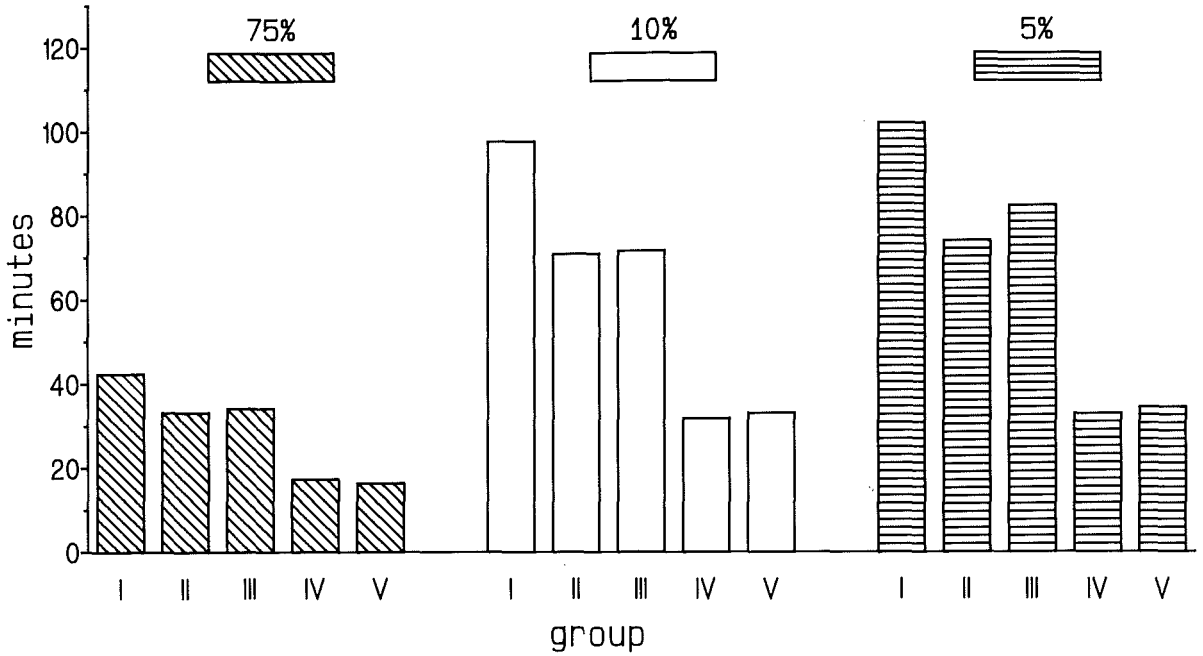


Fig. 20 Calculated recovery time (minutes) of the % EMG depression to 75, 10 and 5% EMG depression after administration of 0.1 $mg.kg^{-1}$ vecuronium. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-13 years

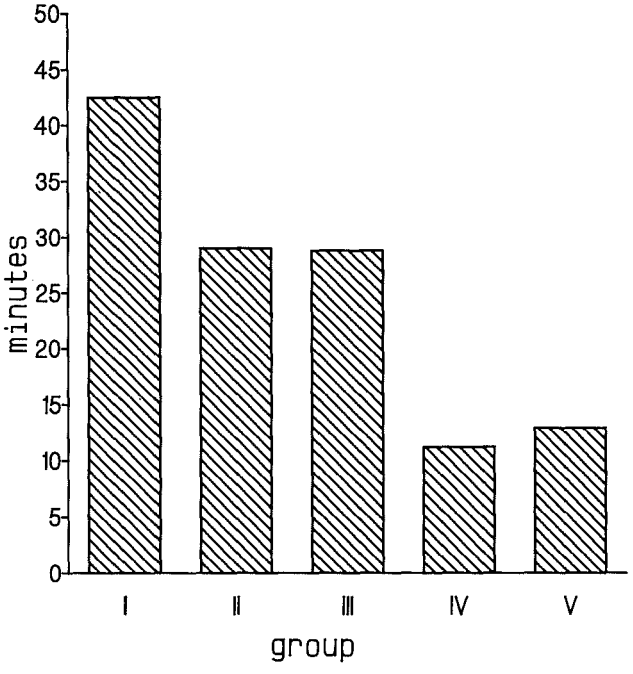


Fig. 21 Calculated recovery rate in minutes (75-25% EMG depression) after administration of 0.1 mg.kg^{-1} vecuronium. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-13 years

Table VII Recovery time (end of injection to 75, 10 and 5% EMG depression) and recovery rate (75-25% EMG depression) after 0.1 mg.kg^{-1} vecuronium in various age groups. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years, group V 6-15 years.

	Calculated (minutes)				Measured (minutes)
	recovery time			recovery rate	recovery rate
	75%	10%	5%		
Group I	42.4	97.7	102.0	42.5	
Group II	33.2	70.9	74.0	29.0	
Group III	34.2	71.6	82.4	28.8	
Group IV	17.3	31.8	32.9	11.2	9.9 ± 2.4
Group V	16.4	33.1	34.4	12.9	10.9 ± 2.6

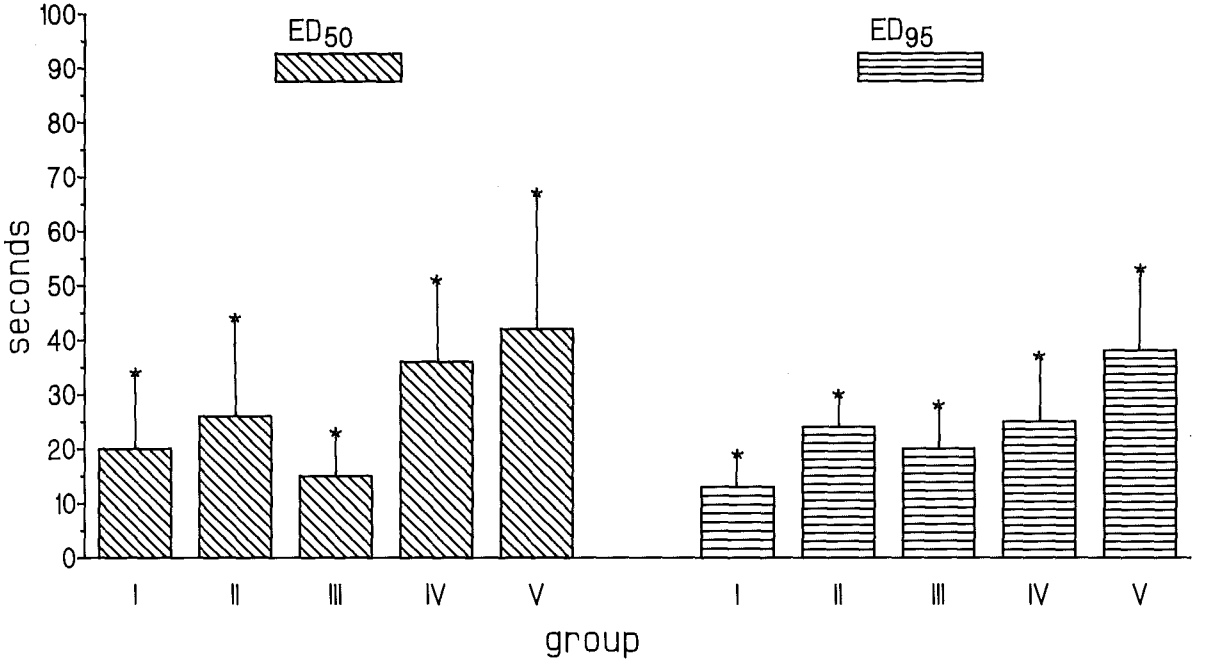


Fig. 22 Latency time in seconds (end of administration to first effect) ± 95% confidence limits after administration of effective dose causing 50 and 95% EMG depression. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-15 years

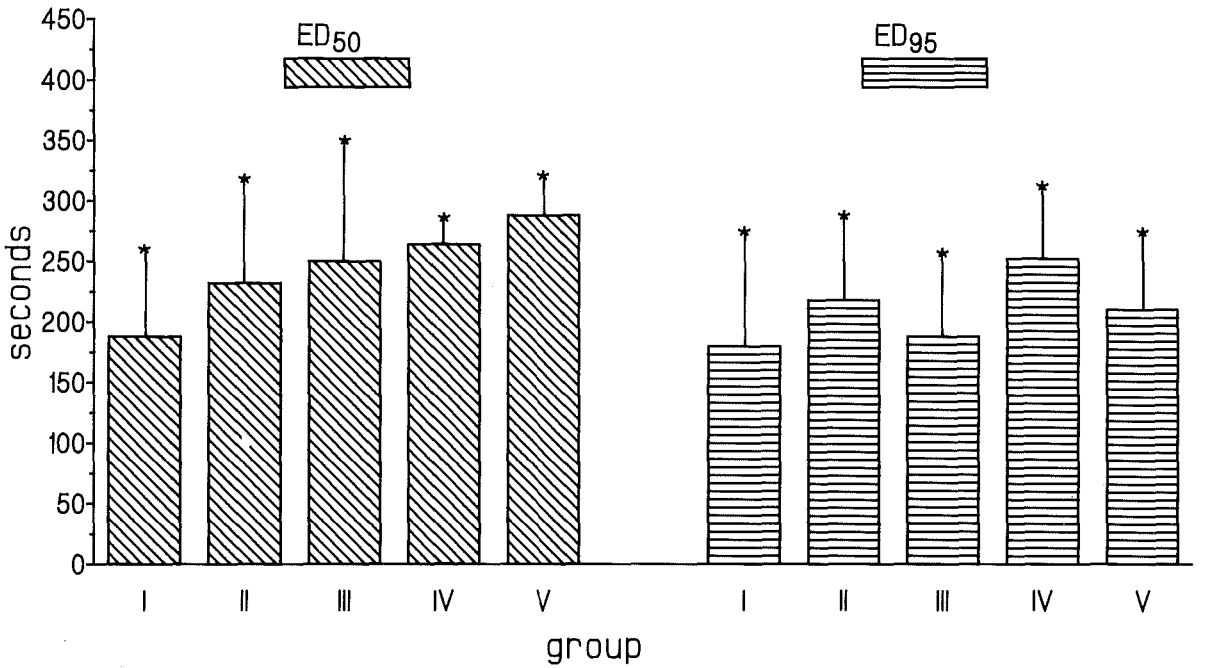


Fig. 23 Onset time in seconds (end of administration to maximal effect) ± 95% confidence limits after administration of effective dose causing 50 and 95% EMG depression. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-15 years

cally significant difference was found between the various age groups nor a correlation between age and onset time (Spearman).

When for the ED_{95} the times are calculated from end of injection to an EMG depression of 90% or over, the "onset" times with the 95% confidence limits in groups I to V are respectively 80 ± 59 sec, 190 ± 104 sec, 116 ± 45 sec, 173 ± 68 sec and 188 ± 90 sec (fig. 24). Here a positive correlation is found between age and "onset" time (alpha = 0.05, Spearman).

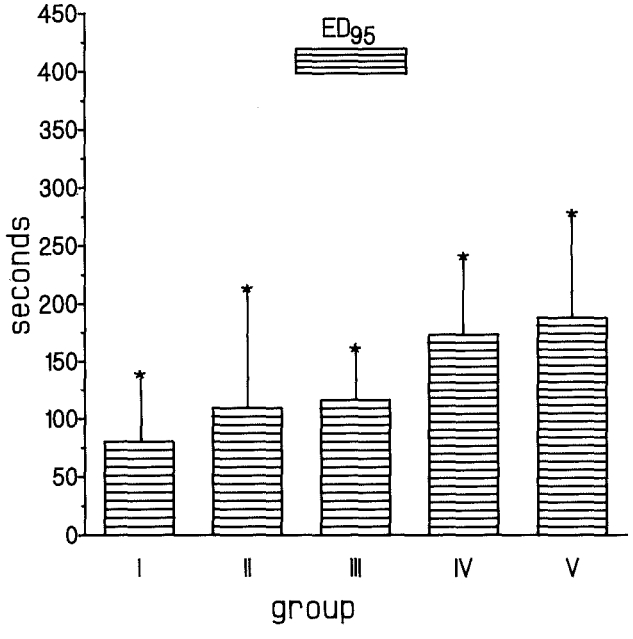


Fig. 24 "Onset time" in seconds (end of administration to ⩾90% EMG depression) ± 95% confidence limits after administration of effective dose causing 95% EMG depression. Group I 0-6 weeks, group II 6-12 weeks, group III 12 weeks-1 year, group IV 1-6 years and group V 6-15 years

DISCUSSION

Comparing the results of our study with others is difficult, because all published paediatric studies on vecuronium pharmacodynamics were conducted under halothane anaesthesia, whereas we strictly avoided halogenated agents. Fisher and Miller (1983) found after a single dose of 70 mcg/kg vecuronium in 6 infants (7-45 weeks old) an onset time of

1.5 min, for 6 children (1-8 years old) 2.4 min and for adults 2.9 min, using MMG. Motsch and colleagues (1985) found after the same dosage an onset time in infants (1 day-10 months old) of 1.4 min and in children (1-6 years old) of 2.7 min using EMG.

For infants these onset times are much shorter than the onset times we found in groups I, II and III after a dose of 60 or 80 mcg/kg. But if the "onset" time is considered to be the time from the end of injection to an EMG depression of 90% or over, the "onset" times of groups I and III resemble the results from Fisher and Miller, and Motsch and colleagues. In group II this "onset" time is still much longer.

For children the measured onset time in our study is also longer than that found by Fisher and Miller, but the onset time after 100 mcg/kg is comparable to the 3.1 min onset time after the same dosage, also using EMG-T1 measurements, as reported by Meistelman and colleagues (1986b). Goudsouzian and coworkers (1983a) found for adolescents an onset time of 1.8 min after 80 mcg/kg, using MMG. This again is a much shorter time than the result we found for adolescents after 100 mcg/kg, even when compared with our defined "onset" time.

The onset time of vecuronium is dependant on the circulation time. Apart from normal individual differences, the circulation time is also influenced by the anaesthetic technique. Halogenated agents have significant cardiovascular effects and also potentiate the neuromuscular blockade of vecuronium. Probably the shorter onset times under halothane anaesthesia are caused by this potentiation and change in tissue perfusion. The differences in monitoring technique are also important. Besides the differences between EMG and MMG there may also be a difference between the EMG onset measured in thenar and hypothenar eminence because of the different percentages of fast and slow fibres.

We also chose to determine the "onset" time, the onset time to 90% blockade or over, because the measurement of the time course to maximal effect is influenced by increasing the sensitivity of the recordings if the blockade approximates 100%. This difference in sensitivity of the recordings may also explain part of the differences in onset time between various studies. Healy et al. (1986) showed that the speed of onset of vecuronium, measuring EMG train-of-four response

under nitrous oxide-fentanyl anaesthesia, does not decrease when giving more than 60 mcg/kg vecuronium. Thus in this way the different results of the various studies cannot be attributed to differences in doses of 70-100 mcg/kg. Comparing the results of the five age groups in our study for the ED_{50} and ED_{95}, no statistically significant differences are found. This may be due to the small numbers of measurements or to the chosen age limits. As we have the clinical impression that the onset time is shorter in younger patients, we also used the Spearman's rank correlation coefficient thus avoiding age limits. We succeeded in confirming our clinical impression with this method. For the ED_{95} the time to 90% injection (or over) proved to be a better choice than the time to maximal effect. The reason for this must be the high sensitivity of the Medelec monitor, which shows even the smallest increase in EMG blockade near the maximal blockade.

Latency times in our study could not be compared with other studies, because no data were collected by other investigators. A study in adults by Gramstad and colleagues (1983) shows a latency time of 51 seconds under nitrous oxide-fentanyl anaesthesia, using MMG. This is much longer than the latency times we found. Comparing our five age groups for latency time, mostly no statistically significant differences were found. But here again the Spearman's rank correlation coefficient confirmed our clinical impression: latency times increase with age. The most plausible explanation for this effect is the increase of circulation time with age.

All recovery data in our study were obtained after a single dose of 0.1 mg/kg vecuronium. In infants (7-45 weeks) Fisher and Miller (1983) found a recovery to 10% blockade after 70 mcg/kg of 73 min during halothane anaesthesia. This resembles our calculated results after 100 mcg/kg in groups II and III. As halothane potentiates vecuronium this explains this similarity. The recovery rate of Fisher and Miller in the infant group is 20 min, and Motsch and coworkers (1985) found 18 min. Both recovery rates are shorter than the 29 min we found in groups II and III, yet in both studies halothane was administered. The recovery in children to 10% blockade after 0.1 mg/kg vecuronium was found to be 35 min by Meistelman and colleagues (1985). They also used EMG and first twitch but also administered halothane. Yet their

findings resemble our 32 min. The recovery rate we measured in children is 10 min. This equals the 10 min found by Goudsouzian and coworkers (1983a) after 80 mcg/kg and by Motsch and colleagues (1985) after the same dose. Both groups of investigators used halothane. Meistelman and colleagues (1986b) found 9.3 min recovery rate after 100 mcg/kg. In adolescents our measured recovery rate of 11 min can be compared with the 13 min recovery rate found by Goudsouzian and coworkers, (1983a) (Table VII).

Comparing our five age groups, group I shows the longest recovery expressed as recovery to 75%, 10% and 5% EMG depression and as recovery rate. In groups II and III the recovery times to 75%, 10% and 5% EMG depression and the recovery rate resemble each other and are shorter than in group I. Obviously changes occur after the first 6 weeks of life. Regarding the ED_{95}'s, as described in Chapter IV, there hardly is a difference between the infants in groups I, II and III. So the differences between groups I, II and III cannot be attributed to a relatively higher dosage in group I. Thus the differences must be due to differences in redistribution or elimination of the relaxant. Body composition changes rapidly in the first months of life (Widdowson, 1981) and liver and kidney function become more mature.

The children and adolescents (groups IV and V) show a much faster recovery than the infants. With age the extracellular fluid volume decreases and thus there is a proportional decrease in the distribution volume of vecuronium. So to achieve a given plasma concentration, a higher dose per kg bodyweight must be administered in the neonates and infants compared to older children and adults. Yet the sensitivity of the neuromuscular system also changes with age. The safety factor increases, thus the sensitivity of the system to vecuronium decreases with increasing age. These factors, together with the maturation of kidney and liver, influence the recovery from neuromuscular blockade. No significant difference is found between groups IV and V but recovery is slightly faster in group IV. The faster recovery in children and adolescents compared to adults can be explained on the basis of enhanced hepatic excretion or metabolic clearance. The difference between groups I, II and III on the one hand and groups IV and V on the other must partly be explained by the difference in the effective

doses. Administering 100 mcg/kg to all groups means a relatively higher dose for groups I, II and III as demonstrated in the results in Chapter IV.

Calculating the recovery times by formula was necessary due to a lack of sufficient patients measured to a recovery of 25% EMG depression. Yet there is a very good correlation between the calculated and measured recovery to 75% EMG depression in groups I to V and between the calculated and measured recovery rate in groups IV and V.

In conclusion the latency and onset times determined in our study are generally longer than the times found in studies performed during halothane anaesthesia. In this study there is a positive correlation for the ED_{50} and the ED_{95} between age and latency and onset times. The calculated recovery times to 75%, 10% and 5% EMG depression and the recovery rate correspond very well with the recovery times in other studies. There also is a good correlation between the calculated and measured data in our study. Recovery is slowest in neonates and slightly faster in infants. The recovery in children and adolescents is twice as fast as that in infants.

VI POTENCY OF VECURONIUM IN RELATION TO AGE

Most studies concerning age-related differences in the pharmacological properties of drugs force the investigator to choose various age groups. Knowledge of physiological changes can lead to a better choice of the age group limits. Such changes seldom occur overnight and one will always be confronted with the interindividual variation. By choosing the wrong age limits, significant differences, although actually present, can be missed. Setting the age-limits, thus, is an arbitrary matter. Therefore we chose a different approach here. Instead of correlating dose and response, a correlation between age and response for a certain dose was studied.

MATERIALS AND METHODS

The results of the dose-response studies of Chapter IV are used for this purpose. For three different doses of vecuronium (0.02, 0.05 and 0.08 mg/kg), all available individuals in all 5 age groups were used and their age and maximal response plotted graphically.

STATISTICAL METHODS

The Spearman's rank correlation coefficient (r_s) is calculated to estimate the association between age and response within a dose group, according to the formula:

$$r_s = 1 - \frac{6R}{n(n^2-1)}$$

$R = \sum d^2$, d is the difference in rank number between age and response and n is the total number of individuals.

RESULTS

The Spearman rank correlation coefficient, calculated for the three chosen doses, shows a negative correlation between age and response.

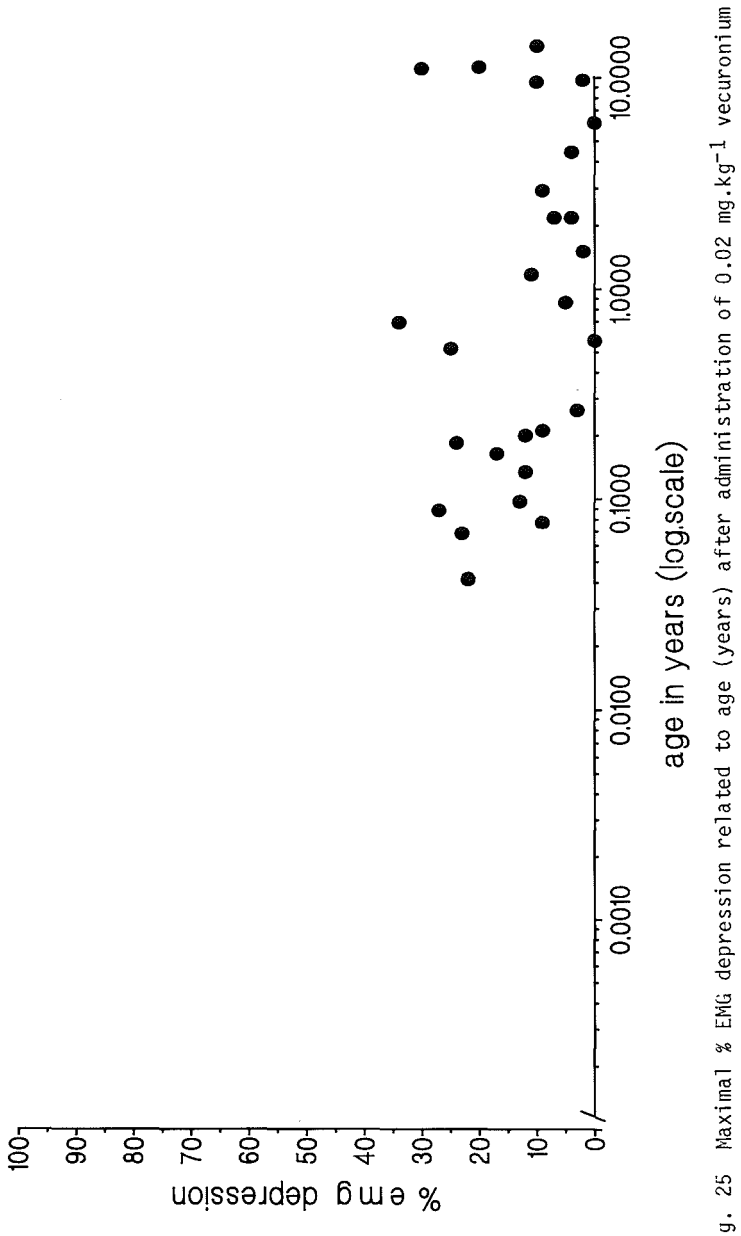


Fig. 25 Maximal % EMG depression related to age (years) after administration of 0.02 mg.kg^{-1} vecuronium

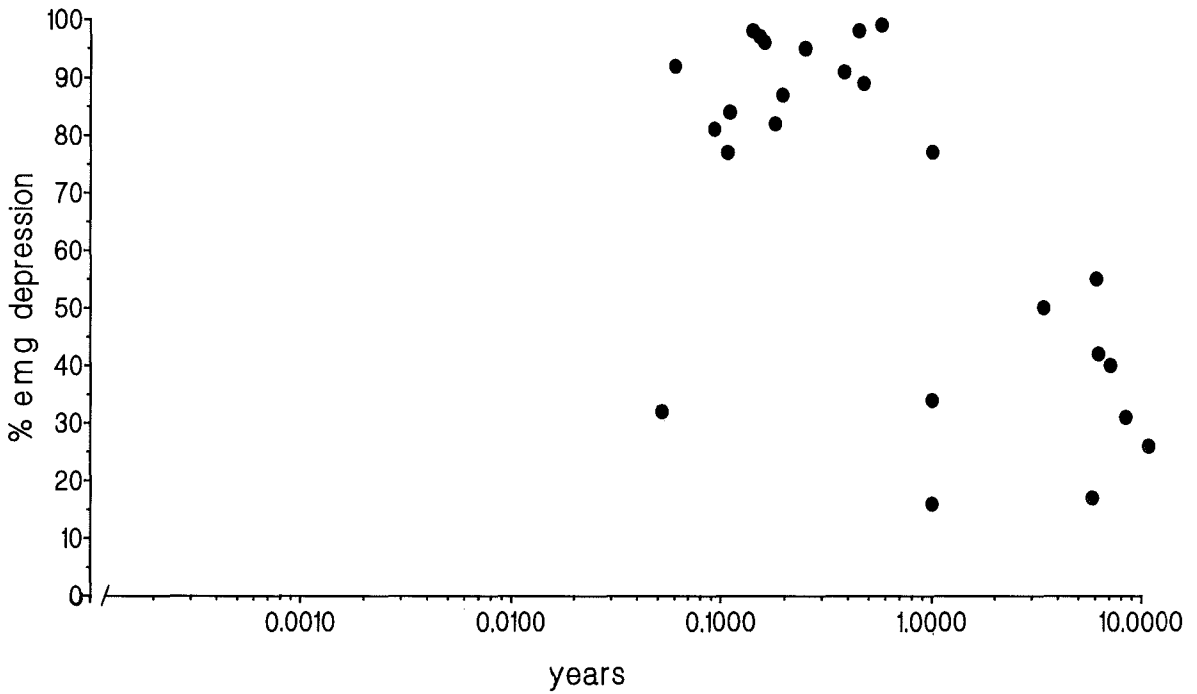


Fig. 26 Maximal % EMG depression related to age (years) after administration of 0.05 mg.kg^{-1} vecuronium

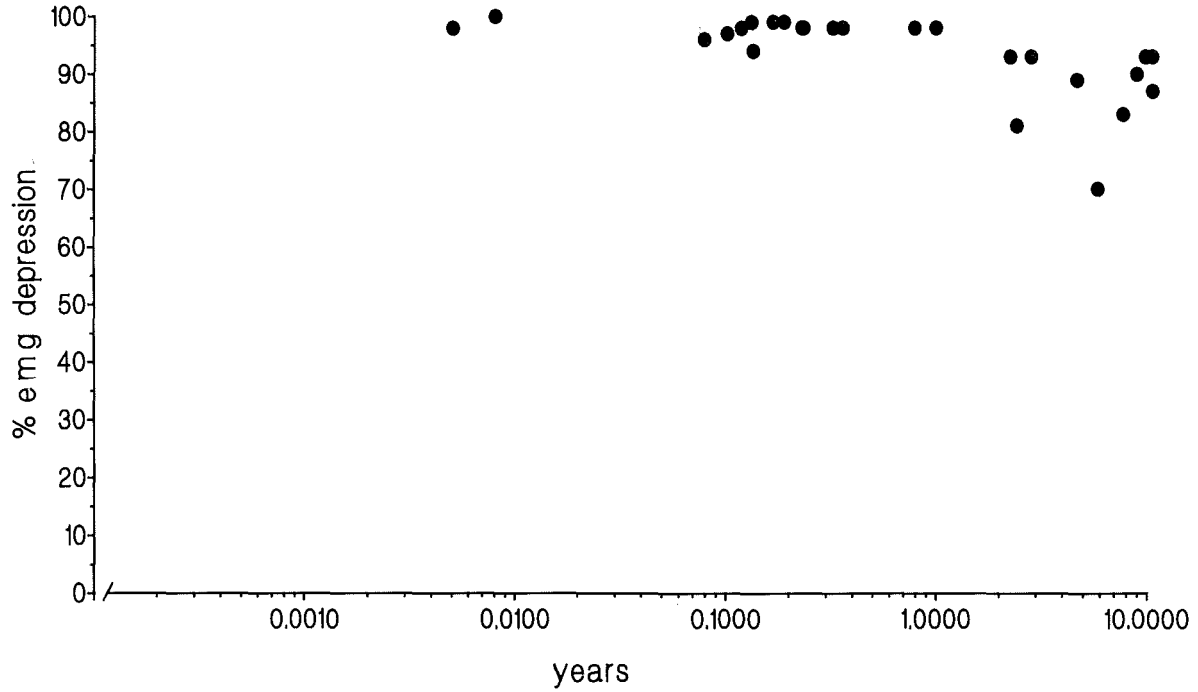


Fig. 27 Maximal % EMG depression related to age (years) after administration of 0.08 $mg.kg^{-1}$ vecuronium

For 0.02 mg/kg (n=27) (fig. 25) $r_s = -0.34$ ($P < 0.10$), for 0.05 mg/kg (n=25) (fig. 26) $r_s = -0.51$ ($P < 0.10$) and for 0.08 mg/kg (n=26) (fig. 27) $r_s = -0.70$ ($P < 0.10$). Thus with increase in age there is a decrease in response with the same dose of vecuronium administered.

DISCUSSION

Ordinary dose-response curves of the potency of vecuronium show a significant difference between infants less than one year old and children over one year of age (Chapter IV). Since this may hide existing differences, avoiding arbitrary age limits is desired. The statistical analysis of the correlation coefficients by Spearman rank correlation, shows ample evidence that such a negative correlation between age and potency of vecuronium exists. This confirms the results of more conventional methods demonstrating the dependence of potency on age.

VII GENERAL DISCUSSION

In spite of all attention paid to the problems concerned with the use of neuromuscular blocking agents, many questions remain to be answered concerning the use of these drugs in paediatric anaesthesia. We performed these studies on vecuronium pharmacodynamics because there is an obvious need, especially in anaesthesia for neonates and infants, for a nondepolarizing neuromuscular blocking agent, that is shorter-acting than the most frequently used agents, such as pancuronium and d-tubocurarine. Because of the total lack of side effects preference was given to vecuronium over atracurium. We limited our studies to the pharmacodynamics and did not extend to the pharmacokinetics, because micromeasurements of plasma concentrations of vecuronium are currently not possible. Moreover because of the high haematocrit of neonatal blood, more than 2 ml of blood is needed to obtain 1 ml of plasma. Samples must be taken within a period of a few minutes to construct a reliable curve in the distribution phase. Thus in neonates and infants a central line must be placed to make this possible. A large number of samples have to be drawn for a pharmacokinetic study so in neonates a blood transfusion would be necessary. These considerations led us to the conclusion that it is not ethical to study plasma levels of vecuronium in neonates and infants so long as micromeasurements of the drug are not possible.

Confusion still remains concerning children's sensitivity to the pharmacodynamics of muscle relaxants. Children are considered to be more (Long and Bachman, 1967), equal (Goudsouzian et al., 1974) or less (Goudsouzian et al., 1975) susceptible to the blocking action of neuromuscular blocking agents. The main cause of these confusing results is the total lack of uniformity in experimental procedure and lack of definition of the term sensitivity. Since sensitivity changes during childhood a strict definition of age groups is also

indispensable. Besides this many factors such as like hypothermia, hypercarbia, hypocarbia, changes in acid-basebalance and administered drugs, can unintentionally influence the effects of nondepolarizing muscle relaxants. Therefore to compare the effects of vecuronium in various age groups we used a uniform procedure, keeping all variables as normal and constant as possible. Unfortunately a group of adults could not be included as our studies were conducted in a paediatric hospital, where adults are not admitted.

Sensitivity can be expressed as potency or as duration of action. Both were determined in our study and led to the following results.
The potency of vecuronium was expressed as the effective dose causing 50, 90 or 95% depression of an evoked response (ED_{50}, ED_{90}, ED_{95}) as measured by electromyography and as dose-response curves in the various age groups. Each patient received only one single dose of vecuronium, since use of a cumulative dose-response technique may lead to an overestimation of the effective dosages of a blocking agent with an intermediate duration of action.
Our results show a marked difference between infants up to 1 year of age (groups I, II and III) on the one hand and children above 1 year of age (groups IV and V) on the other. The $ED_{50, 90}$ and $_{95}$ in groups IV and V are approximately 1.6 times the $ED_{50, 90}$ and $_{95}$ of groups I, II and III. Yet there is a remarkable resemblance between the effective dosages between groups I, II and III and the same is found between groups IV and V. The measured dose (mg/kg)-response (% EMG depression) curves and the calculated dose (ln mg/kg)-response (probit % EMG depression) curves show the same resemblance between groups I, II and III on the one hand and between groups IV and V on the other. The slopes of all five curves are practically equal. Thus the interindividual variation does not vary between the five age groups. The clinical impression that neonates and infants show the most interindividual variation could not be confirmed.

The potency of vecuronium is partly determined by the amount of extracellular fluid as it distributes throughout the extracellular fluid before reaching the receptor sites (Boreus, 1982; Roland, 1978). A larger volume of distribution will result in a lower concentration and thus a lesser effect. Whether this is the reason for the differen-

ce we demonstrated in our study between the two groups aged below and above 1 year of age, cannot be answered because we could not perform pharmacokinetic studies. However the results of studies by Fisher and collegaues clearly demonstrated a larger distribution volume for vecuronium in infants (3-11 months of age) as compared to children (1-5 years of age) (Fisher et al., 1985a,b). Similar results were found for atracurium by Brandom and colleagues for infants (1-8 months of age) and children (2-10 years of age) (Brandom et al., 1986). Fisher and colleagues found the steady-state distribution volume of d-tubocurarine in neonates (0-2 months of age) to be significantly larger than in infants (2-12 months of age), and in infants to be larger than in children (1-12 years) (Fisher et al., 1982). On basis of the extracellular fluid one would expect major changes to occur during the first year of life since, in this period the extracellular fluid is decreasing most (Widdowson, 1981). Thus with increasing age less drug per kg bodyweight is needed to reach the same plasma concentration. There may also be a difference in sensitivity of the neuromuscular system to the neuromuscular blocking action of vecuronium.

The sensitivity of the neuromuscular system for other relaxants decreases with age. Maturation of the system occurs in the first 2-3 months after birth (Goudsouzian, 1980; Crumrine, 1981). Such a point could be proven if the plasma concentrations at which a certain degree of neuromuscular blockade exists differ between the various age groups. For reasons already described we unfortunately were not able to demonstrate this. From the literature however it can be concluded that the balance between immaturity of the neuromuscular system and the increased extracellular fluid favors the former in neonates. Yet it is surprising that the same pharmacodynamic results were found in our study for infants from 12 weeks-1 year of age but that yet another clear division is found between infants up to 1 year of age and children of 1 year and older. Therefore other unexplained mechanisms that undergo changes around the age of 1 year must exist and be involved in determining the potency of vecuronium.

The only study on vecuronium in infants (7-45 weeks of age) determining the ED_{50} was performed by Fisher and Miller (1983). They

compared infants with children (1-8 years of age) and adults under halothane anaesthesia using MMG. Adults have the lowest ED_{50}, followed by neonates and the highest ED_{50} is found in children. But no statistically significant difference was found and all three age groups were considered equally sensitive. Perhaps if they had analyzed their data by Spearman's rank correlation they also would have found a statistically significant correlation between potency and age. Goudsouzian and colleagues (1983a) found children (2-9 years of age) significantly more resistant to the neuromuscular effects of vecuronium than adolescents (10-17 years of age).

More comparisons between various age groups were made for the effective dosages of atracurium. Neonates (1-28 days old) were studied by Meakin and coworkers (1987) and were found to be more sensitive than infants (1 month-1 year old), infants were found to be more sensitive than children (1-5 years old). Infants were also studied by Meistelman and colleagues (1986a). They found infants of 1-3 months of age more sensitive to atracurium than infants of 3-12 months of age. Brandom and coworkers (1984) found infants (1-6 months of age) to be equally sensitive as adolescents (11-16 years old) and both these age groups more sensitive to atracurium than children (2-10 years old). Goudsouzian and colleagues (1985) however found no difference in sensitivity to atracurium between infants (4 weeks-1 year old), children (1-10 years old) and adolescents (11-17 years old).

Other muscle relaxants were studied by Goudsouzian and colleagues (1984). They found children (1-15 years old) more resistant than adults to pancuronium, metocurine and d-tubocurarine. The discrepancy in the results between the various relaxants, in our opinion, reveals that the potency of relaxants is multifactorially determined and not only dependent on extracellular volume and maturation of the neuromuscular junction.

Sensitivity can also refer to (clinical) duration or recovery rate. We determined the time from the end of injection of 0.1 mg/kg vecuronium to 75, 10 and 5% EMG depression (recovery time), the time from 75-25% EMG depression (recovery rate) and the slope of the recovery in all five age groups. The recovery was always slowest in the neonates (group I), followed equally by the infants (groups II and

III). Recovery in children and adolescents (groups IV and V) was twice as fast. Using the calculated slope of the recovery as parameter the same results were found. Neonates recover very slowly, followed by the infants, and a much faster recovery is seen in children and adolescents. These results indicate that metabolism and/or excretion of vecuronium increases with age. It is assumed that this coincides with the optimalisation of liver and kidney function from neonates to adolescents, as described by various authors (Fisher et al., 1985a; Motsch et al., 1985). Vecuronium depends for its plasma elimination on redistribution (i.e. liver uptake), metabolism (liver) and excretion (hepatic and renal). Thus these factors may influence the duration of action of vecuronium. Since atracurium is reported to solely depend on Hofmann degradation in the plasma it is expected to be less age-dependent than vecuronium. This is however not confirmed by the literature (discussed below).

Between groups I, II and III there is no significant difference in ED_{95}. Thus the differences in recovery cannot be attributed to relatively higher doses, but may be due to differences in redistribution, elimination or other mechanisms. The faster recovery of groups IV and V is partly explained by the fact that expressed as effective dose the given 0.1 mg/kg is less in groups IV and V.
However the recovery rate for vecuronium is also much faster in groups IV and V. The recovery times to 90% of control found in infants (7-45 weeks old) and in children (1-8 years old) by Fisher and Miller (1983) resemble our results, as does their reported recovery rate in children. However the recovery rate in infants reported by Fisher and Miller (1983) and Motsch and coworkers (1985) is faster than our calculated rate. Yet in both studies the recovery of children is significantly faster than the recovery of infants. Goudsouzian and colleagues (1983a) studied vecuronium in children (2-9 years old) and adolescents(11-17 years old) and found no significant differences in recovery times between these two age groups. Generally no major differences are found in recovery times between children, adolescents and adults when comparing different studies. Yet no study on vecuronium compares children or adolescents to adults.

Atracurium is a nondepolarizing neuromuscular blocking agent that

has been uniquely designed to undergo degradation at physiological temperature and pH by a self-destroying mechanism called "Hofmann elimination" (Hughes, 1986). Thus, to reiterate, it is not surprising that Brandom and colleagues (1984) found totally different results in the comparison of recovery times of various age groups after atracurium and after vecuronium. The recovery times of neuromuscular transmission after atracurium administration to 25, 50 and 95% of the control value are significantly shorter in infants than in older children or adolescents at equal multiples of the ED_{95}. Meretoja and Kalli (1986b) however found different results for atracurium. Although also using EMG and first twitch they found recovery times to 10 and 100% significantly longer in patients under 10 kg body weight than in heavier patients. Also the recovery rate in patients under two months of age is significantly longer than in older infants, children and adolescents. Goudsouzian and coworkers (1983b) did not find a difference in recovery times of atracurium between children (2-10 years old) and adolescents (11-17 years old).

The latency and onset times of vecuronium in our study show a positive correlation with age. Fisher and Miller (1983) and Motsch and colleagues (1985) also found the shortest onset times in infants. These results are very well explained by the decreased circulation time in infants. Goudsouzian and coworkers (1985) studied the onset time of atracurium. In infants (4 weeks-1 year old) the onset time is shorter than in children (2-10 years old) and adolescents (11-17 years old). No difference was found between children and adolescents. Lavery and Mirakhur (1984) compared onset times of atracurium, vecuronium and pancuronium in children of 1-14 years of age. The onset times of atracurium and vecuronium are similar and shorter than the onset time of pancuronium.

From our studies the following clinical conclusions can be drawn:

- The potency of vecuronium in neonates and infants is higher than in children and adolescents. The effective dosages in children and adolescents are approximately 1.6 times the effective dosages in neonates and infants. Thus in children less than 1 year of age lower dosage should be used.

- The recovery times for vecuronium to a certain percentage of EMG depression and the recovery rate are very long in neonates. The recovery is faster in infants than in neonates. But the recovery in children and adolescents is twice as fast as the recovery in infants.
- Long acting neuromuscular blocking agents such as d-tubocurarine and pancuronium must be considered obsolete for use in anaesthesia in children younger than one year of age, because of the very slow recovery of these drugs and the extreme sensitivity of neonates and infants to residual neuromuscular blockade. The drugs of choice in these age groups are the neuromuscular blocking agents of intermediate duration: vecuronium and atracurium.
- Latency and onset times of vecuronium increase with increasing age. In no age group did the onset time of vecuronium equal the fast onset of succinylcholine as reported in the literature (Cunliffe et al., 1986).
- No side effects of vecuronium were observed in any of the age groups.
- Vecuronium is a safe drug for use in paediatric anaesthesia.

VIII SUMMARY

Since the introduction of muscle relaxants in clinical paediatric anaesthesia (Chapter I) controversies concerning their potency and pharmacodynamic behaviour have remained. Over the years it has been demonstrated that various factors influence the neuromuscular transmission. During growth from newborn to adulthood many of these factors change due to the process of maturation. Apart from changes in organ functions such as liver and kidneys, body composition is also undergoing constant change. All these changes will influence on pharmacokinetic parameters and thus the pharmacodynamic behaviour of the neuromuscular blocking agents. Until recently information about the potency and pharmacodynamics of muscle relaxants in neonates and infants has been scarce due to the problems in quatitation of neuromuscular blockade in these age groups (Chapter II). With the development of electromyographic quantitation of neuromuscular blockade more information has become available but, due to remaining inconsistency in anaesthetic technique and many other factors, comparison between the various studies is almost impossible. This has led to different recommendations concerning the use of muscle relaxants in paediatric anaesthesia. For example, some authors consider neonates resistent to nondepolarizing muscle relaxants, others more sensitive and yet others consider them to be equally sentitive to these drugs as adults. In our study we determined and compared the potency and pharmacodynamic behaviour of vecuronium bromide, an intermediately long-acting nondepolarizing muscle relaxant, in the various paediatric age groups under similar anaesthetic conditions and using the same electromyographic method (EMG) for quantitation of neuromuscular blockade. From the various currently used nondepolarizing muscle relaxants we decided to study vecuronium bromide because of its minimal adverse effects compared to

other relaxants (Chapter III).

In the first clinical study we determined the potency of vecuronium bromide (Chapter IV). There was no significant difference in potency between neonates (birth-6 weeks) and infants of either 6-12 weeks and 12 weeks-12 months of age. Above that age the potency of vecuronium was statistically significantly lower both in children (1-6 years), and in older children and adolescents (6-14 years). There was no difference between the last two groups. In our opinion the potency of vecuronium as described in the literature for adults is slightly higher than the potency we found in the groups older than 1 year. It must be realised however that the age groups are arbitrary chosen. If, in order to avoid such an arbitrarily division of patients, a Spearman's rank correlation coefficient is calculated for potency and age, a negative correlation is found. This indicates that with increase in age a decrease in potency occurs (Chapter VI).

In our second study we determined the pharmacodynamic parameters (latency time, onset time, duration of action and recovery rate) in the same age groups (Chapter V). A significant difference between the various age groups could not be demonstrated for latency time (time from administration to first EMG depression) and onset time (time from administration to maximal effect). However the Spearman's rank correlation coefficient demonstrated a positive correlation between these parameters and age. The duration of action, defined as time to recovery to 10% depression of the EMG was significantly longer in neonates than in infants, which had values which were significantly longer than in children and adolescents. The same differences were found for the recovery times from administration to 75% and 5% EMG depression. The recovery rate (time from 75-25% EMG depression) was significantly longer in neonates as compared to infants, in which it was significantly longer than in children and adolescents.

From our studies we believe it to be justified to conclude (Chapter VII) that neonates and infants are more susceptible to vecuronium bromide than children and adolescents. Recovery from vecuronium bromide in neonates is very slow, resulting in a long duration of action. Only above 1 year of age does vecuronium bromide reach its

intermediate duration of action, as is known in adults.
Whether our results can be extrapolated to other neuromuscular blocking agents is not known. However, due to the large variability in their metabolic and excretory pathways, as well as in their pharmacological mechanism of action (pre-junctional and post-junctional effects) differences can be expected.

SAMENVATTING

Sinds de introductie van spierrelaxantia in de klinische kinderanesthesie (hoofdstuk I) hebben er meningsverschillen bestaan over hun werkingssterkte en farmacodynamisch gedrag. Gedurende de afgelopen jaren is het aangetoond dat verschillende factoren de neuromusculaire transmissie beinvloeden. Tijdens de groei van pasgeborene tot volwassene veranderen vele van deze factoren als gevolg van rijping. Daarbij veranderen orgaanfuncties zoals die van lever en nier en lichaamssamenstelling voortdurend. Deze veranderingen hebben invloed op de farmacokinetische parameters en dus op het farmacodynamische gedrag van spierrelaxantia. Tot voor kort was informatie over de werkingssterkte en farmacodynamiek van spierrelaxantia in neonaten en zuigelingen schaars door de bestaande problemen betreffende het kwantificeren van spierverslapping in deze leeftijdsgroepen (hoofdstuk II). Met de ontwikkeling van elektromyografische kwantificering van spierverslapping kwam er meer informatie beschikbaar, maar vanwege de blijvende inconsequentie in anesthesie techniek en vele andere fatoren, is vergelijking tussen de verschillende onderzoeken bijna onmogelijk. Dit heeft geleid tot verschillende aanbevelingen voor het gebruik van spierrelaxantia in de kinderanesthesie. Sommige schrijvers beschouwen pasgeborenen als resistent voor niet-depolariserende spierrelaxantia, andere als gevoeliger en weer andere beschouwen ze als even gevoelig voor deze farmaca als volwassenen.

In ons onderzoek hebben we de werkingsduur en het farmacodynamische gedrag van vecuronium bromide, een middellang werkend niet-depolariserend spierrelaxans, bepaald in de verschillende leeftijdsgroepen van kinderen onder dezelfde anesthesie omstandigheden en gebruik makend van dezelfde elektromyografische methode (e.m.g.) ter kwantificering van spierverslapping. Van de verschillende huidig gebruikte niet-depolariserende spierrelaxantia hebben we besloten tot het bestuderen van

vecuronium bromide vanwege zijn minimale bijwerkingen vergeleken met andere relaxantia (hoofdstuk III).

In het eerste klinische onderzoek hebben we de werkingssterkte van vecuronium bromide bepaald (hoofdstuk IV). Er was geen significant verschil in werkingssterkte tussen pasgeborenen (geboorte tot 6 weken) en zuigelingen van 6 tot 12 weken en 12 weken tot 12 maanden oud. Boven die leeftijd was de werkingssterkte van vecuronium statistisch significant lager, zowel in kinderen van 1 tot 6 jaar als in kinderen van 6 tot 14 jaar. Er bestond geen verschil tussen deze laatste twee groepen. Naar onze mening is de werkingssterkte van vecuronium in volwassenen zoals beschreven in de literatuur, een beetje groter dan de werkingssterkte, die wij gevonden hebben in de groepen van 1 jaar en ouder. Men moet zich echter realiseren, dat leeftijdsgroepen arbitrair gekozen worden. Als men, om zo'n arbitraire verdeling van patiënten te voorkomen, een Spearman's rangorde correlatie coëfficiënt berekent voor werkingssterkte en leeftijd, dan vindt men een negatieve correlatie. Dit betekent, dat met toename van de leeftijd een daling in werkingssterke optreedt (hoofdstuk VI).

In ons tweede onderzoek hebben we de farmacodynamische parameters (latentie tijd, inwerkingstijd, werkingsduur en herstelsnelheid) in dezelfde leeftijdsgroepen bepaald (hoofdstuk V). Een significant verschil tussen de verschillende leeftijdsgroepen kon niet worden aangetoond voor de latentietijd (tijdsduur van toediening tot eerste e.m.g. depressie) en inwerkingsduur (tijdsduur van toediening tot maximaal effect). De Spearman's rangorde correlatie coëfficiënt toonde echter een positieve correlatie tussen deze parameters en leeftijd aan. De werkingsduur gedefinieerd als tijdsduur van toediening tot een herstel tot 10% e.m.g. depressie, was significant langer in pasgeborenen dan in zuigelingen, die op hun beurt weer een significant langere werkingsduur vertoonden dan kinderen van een jaar en ouder. Dezelfde verschillen werden gevonden voor het herstel tot 75% en 5% e.m.g. depressie. De herstelsnelheid (tijdsduur van 75 tot 25% e.m.g. depressie) was significant langzamer in pasgeborenen vergeleken met zuigelingen en in zuigelingen weer significant langzamer dan in kinderen van 1 jaar en ouder.

Wij menen uit onze onderzoeken te mogen concluderen (hoofdstuk VII) dat pasgeborenen en zuigelingen gevoeliger zijn voor vecuronium bromide dan kinderen van 1 jaar en ouder. Het herstel van vecuronium bromide in pasgeborenen is erg langzaam, resulterend in een lange werkingsduur. Pas boven de leeftijd van 12 maanden bereikt vecuronium een middellange werkingsduur zoals die gezien wordt bij volwassenen. Of onze resultaten geëxtrapoleerd kunnen worden naar andere spierrelaxantia is onbekend. Echter, omdat er een grote variabiliteit bestaat in hun metabolisme en excretie, evenals in hun farmacologisch werkingsprincipe (prejunctionele and postjunctionele effecten), kan een verschil verwacht worden.

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De schrijfster van dit proefschrift werd op 12 augustus 1951 te Utrecht geboren. Zij doorliep de eerste drie klassen van de Gemeentelijke H.B.S. te Hilversum en slaagde in juni 1968 voor het eindexamen H.B.S.-B aan het Stedelijk Lyceum te Zutphen. Zij studeerde geneeskunde aan de Rijksuniversiteit te Groningen en behaalde daar in augustus 1973 het doctoraal examen. Haar junior- co-assistentschappen doorliep zij in het Algemeen Stads- en Academisch Ziekenhuis te Groningen en haar senior- co-assistentschappen in het ziekenhuis Ziekenzorg te Enschede, waarna in november 1974 het arts diploma werd behaald.

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